Bladder cancer:

diagnosis and management

NICE Guideline 2

Evidence Review

Developed for NICE by the National Collaborating Centre for Cancer

Contents

1 Patient Centred Care

1.1 Patient satisfaction

Review question: What are the causative and contributory factors that result in the comparatively low levels of reported patient satisfaction (c.f. the National Patient Satisfaction Surveys) for bladder cancer patients within the group of urological cancers?

Rationale

There are many differences in the experiences of bladder cancer patients and their families in relation to the information and support received during diagnosis, treatment, and into end of life care. Within the National Cancer Patient Experience Survey there appears to be a significant qualitative/quantitative difference in the reported patient experience between Prostate Cancer patients and Urological Cancer (including Bladder Cancer) patient groups. However, both sets of patients are treated within the same urological services. This strongly suggests a need for further specific research into patient reported outcomes of bladder cancer patients.

Question in PICO format

Sample	Phenomenon of interest	Evaluation
Patients with bladder cancer	Patient satisfaction in the National Cancer Patient Experience Surveys	Areas where urological cancer patients report lower satisfaction than other cancer groups.

METHODS

Information sources

This review question was answered by reviewing the National Cancer Patient Experience Survey (NCPES) 2011/12 – National Report, published by the Department of Health. The surveys are designed to monitor national progress on improving outcomes in cancer patient experience. A literature search was also performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

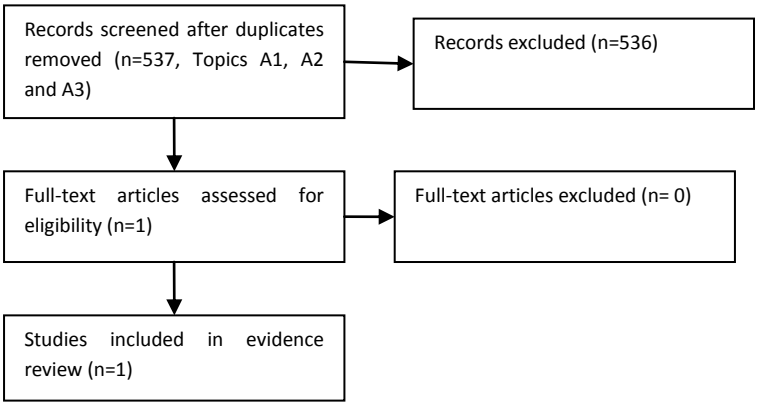
Data synthesis

Areas in the NCPES which had less positive assessments by cancer patients were reported. Also, areas which urological cancers patients (excluding prostate cancer) rated lower than other cancer groups were reviewed, which provides some indication as to the overall comparatively lower levels of patient satisfaction within the urological cancers group.

RESULTS

Result of the literature searches

Figure 1. Study flow diagram



Study quality and results

The literature search yielded one study reporting an analysis of treatment decision making data from the 2010 NCPES (El Turabi *et al.*, 2013).

Evidence statements

Data from the NCPES 2011/12 National Report was used to answer this review question. Compared to other cancer patients, urological cancer patients were least likely to be offered a written assessment and care plan or to be provided with information about self-help or support groups. Urological cancer patients were also least likely to be given the name of a CNS (Table 1.). There were pronounced differences in views between those patients with a CNS and those without one in terms of verbal and written information, involvement, information on financial support and prescriptions, discharge information, post discharge care, and emotional support. This indicates that the presence of a CNS makes a positive difference to the perceived quality of cancer services and may be a reason for the comparatively low levels of patient satisfaction for urological cancer patients. In an analysis of responses to one question from the 2010 NCPES, one study (El Turabi *et al.*, 2013) reported that bladder cancer patients were among the least likely to report a positive experience of involvement in treatment decision making (see Table 2).

Table 1. Areas in the NCPES where urological cancer patients gave less positive assessments (less than average scores) as compared to other cancer groups

NCPES question	Average (range) % across all cancer groups	Urological cancers %
When you were first told that you had cancer, had you been told you could bring a family member or friend with you?	72% (61% to 80%)	65%
Given written information about the type of cancer that they had which was easy to understand?	69% (50% to 78%)	66%
Given a choice of different types of treatment?	84% (75% to 90%)	75%
Do you think your views were taken into account when the	70% (64% to 76%)	65%

NCPES question	Average (range) % across all cancer groups	Urological cancers %
team of doctors and nurses caring for you were discussing which treatment you should have?		
Were the possible side effects of treatment(s) explained in a way you could understand?	75% (69% to 79%)	69%
Were you given written information about the side effects of treatment(s)?	81% (67% to 90%)	70%
Were you given the name of a Clinical Nurse Specialist who would be in charge of your care?	87% (75% to 93%)	75%
Did hospital staff give you information about support or self-help groups for people with cancer?	82% (65% to 89%)	65%
Did hospital staff give you information about how to get financial help or any benefits you might be entitled to?	52% (29% to 70%)	29%
Did hospital staff tell you that you could get free prescriptions?	73% (50% to 82%)	61%
After leaving hospital, were you given enough care and help from health or social services (For example, district nurses, home helps or physiotherapists?	61% (51% to 68%)	51%
Have you been offered a written assessment and care plan?	24% (20% to 27%)	20%

Table 2. Variation of patient experience of involvement in treatment decision making within urological cancers (El Turabi et al., 2013)

	% reporting most positive experience	Adjusted odds ratio*	95% CI
Bladder (n=3868)	68.7	Ref	
Prostate (n=3882)	74.1	1.28	(1.16–1.42)
Renal (n=528)	75.2	1.46	(1.18–1.80)
Testicular (n=228)	74.1	1.96	(1.43–2.69)

*Higher values indicate more likely to report positive experience of shared decision making. An OR >1 for a category shows that patients of that category are more likely to report positive experience than the reference group; an OR <1 shows patients of that category are less likely to report positive experience than the reference group

References to included studies

El Turabi, A. et al. Variation in reported experience of involvement in cancer treatment decision making: Evidence from the National Cancer Patient Experience Survey. British Journal of Cancer 2013; 109(3): 780-787.

National Cancer Patient Experience Survey 2011/12 - National Report, Department of Health, 2012

Evidence tables

Study, country	Population	Method	Results	Additional comments
El Turabi 2013 UK	2010 English NHS Cancer Patient Experience Survey. Sent to all adult patients with a primary diagnosis of cancer who were treated in a hospital as an inpatient or day-case patient in the first quarter of 2010. 41,441 patients with a primary tumour diagnosis and complete sociodemographic data were analysed if they provided an informative response to the single question evaluating the experience of involvement in decisions about treatment: 'Were you as involved in decisions about which treatment you would have as you wanted?' 3868 respondents with bladder cancer.	Binary responses to the treatment decision making question were analysed to compare most positive responses ' yes definitely' to less positive responses 'yes, to some extent' and 'no but I would like to have been more involved' The proportion of patients in each sociodemographic group and cancer type who reported the most positive experience of involvement in treatment decision making and calculated respective unadjusted odds ratios using logistic regression To examine whether any observed variation was because of confounding by patient factors, data was adjusted for all observed sociodemographic variables and cancer type using a multivariable fixed-effects logistic regression model (model 2). Then, to examine whether any variation was explained by clustering of patients from certain groups in hospitals with lower or higher than average performance, we constructed a mixed-effects model, augmenting model 2 with a random effect (intercept) for hospital of treatment (model 3). Also performed two extreme case scenario sensitivity analyses whereby all excluded respondents were assumed to have provided informative responses, either all indicating a positive experience or all indicting a negative experience.	29776 (72%) reported the most positive experience of involvement in treatment decision making, 9197 (22%) reported conditionally positive experience and 2468 (6%) reported definitely negative experience. unadjusted analysis of different patient groups (model 1) -Among the group of most common cancers, patients with melanoma were substantially more likely to report the most positive experience than patients with other cancers (unadjusted OR melanoma vs colon 1.28; P<0.001), whereas patients with anal cancers, myeloma and bladder cancer reported the most negative experience (unadjusted OR vs colon 0.49, 0.61, and 0.61 respectively; P<0.001). There was no evidence of differences in reported experience between sexes (unadjusted OR women vs men 0.98; P=0.463). Between different age groups there was strong evidence of substantial variation (P<0.001); patients in the 65–74 age group reported the most positive experience, whereas younger patients reported substantially less positive experience (unadjusted OR 16–24 vs 65–74 0.48), as did patients older than the 65–74 age group (unadjusted OR 85+ vs 65–74 0.77). There was strong evidence that patients from ethnic minorities were more likely to report a negative experience than White patients (unadjusted OR vs White: Black 0.48, Chinese 0.57, South Asian 0.67; P<0.001). Experience also varied between patients of differing socioeconomic backgrounds (P<0.001), but the magnitude of this variation was small (unadjusted OR most deprived vs least deprived 0.87). None of the above findings changed substantially when hospital of treatment was included as a random effect (model 3) suggesting that the observed variation was unlikely the result of clustering of certain patient groups into hospitals with higher or lower performance. Extreme case scenario sensitivity analyses about the potential impact of differential perception or recall of shared decision making produced similar findings for demographic variables to those observed in the main analysis. Within-specialty variation were observed for colorectal, gynaecological and urological cancers, with patients with rectal, ovarian and bladder cancer reporting notably worse experience than patients with colon, uterine and renal cancers, respectively	There was no option for respondents to highlight dissatisfaction with over-involvement in treatment decision making. Also not able to assess whether doctors did indeed present all respondents with appropriate choice of treatment where such a choice was clinically appropriate (the consultation style of some treating clinicians may involve little shared decision making with the patient)

1.2 Role of the clinical nurse specialist in giving information and advice

Review question: Which elements of the information and support provided by clinical nurse specialists (CNS)/key workers are most important for bladder cancer patients and/or their carers, at the various stages of the patient pathway?

Rationale

The clinical nurse specialist (CNS) or key worker has significant input into the provision of information and support for cancer patients and the resultant reported levels of patient satisfaction. It is important to identify which elements of information and support provided by CNS's are most important to bladder cancer patients.

Question in PICO format

Sample	Phenomenon of interest	Evaluation
Patients with bladder cancer & their carers	Information & support provided by a clinical nurse specialist or key worker	• Patient and/or carer satisfaction (with communication, information support and treatment received) • Health-related quality of life (inc. patient and carer-reported outcomes) • Understanding/knowledge of disease and treatment • Psychological factors (e.g. distress, coping) • Perceived social support • Informed choice and decision-making • Ability to self-manage condition/side-effects • Referral to support groups/networks

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

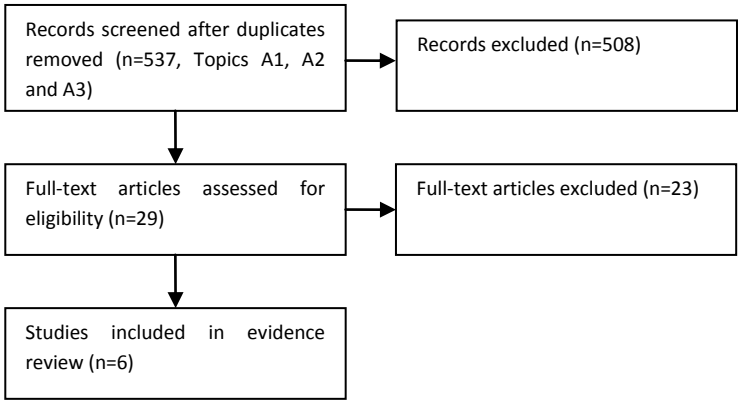
Data synthesis

Evidence from qualitative studies and cross-sectional questionnaire studies was appraised using the NICE methodology checklist for qualitative studies. A narrative summary of the evidence was presented.

RESULTS

Result of the literature searches

Figure 2. Study flow diagram



Study quality and results

Six studies were identified for this evidence review. Three studies were qualitative interview studies, two studies used questionnaires to collect data, and one study reported the results from a randomised trial. A summary of the included studies is provided in Table 3.

Evidence statements

In four studies (Fitch *et al.,* 2010; Mansson *et al.,* 1991; Kressin *et al.,* 2010; Ronaldson*,* 2004), data were collected from bladder cancer patients who had undergone radical cystectomy. Common physical and psychological post-operative issues reported by patients included the ability to self-manage urinary diversion, adjustment to body image, and changes in sexual function. In one UK study (Dearing, 2005) of 78 patients with superficial bladder cancer (pTa or pT1), 47% were aware of their underlying diagnosis. 33% of the 55 smoking patients had been told to stop smoking by their general practitioner and 7% had been told to stop by their urologist. Faithful *et al.* (2001) reported patient satisfaction and quality of life from a randomised trial of nurse-led or conventional follow-up in men treated with radical radiotherapy for prostate or bladder cancer. The nurse-led protocol focused on coping with symptoms and provided continuity of care and telephone support. There were few differences between groups in terms of overall quality of life. However, men in the nurse-led group were significantly more satisfied with their follow-up care than men in the control group. The nurse-led clinic was perceived as providing a greater amount of information. Patients liked the continuity of care provided and the fact that their families could be included in the consultation.

Table 3. Summary of included studies

Study	Population	Methods	Analysis	Relevance to guideline population	Key findings
Fitch *et al.* (2010)	Well reported	Well reported	Well reported and rigorous analysis	Canadian cohort. Patients interviewed after cystectomy and urinary diversion to explore experiences and perceptions of living with changes following surgery.	Adjustments to body image, sexual function, management of incontinence or leakage were important issues for patients. Patients wanted more information about what to expect after urinary diversion and how to self-manage post-

					operative problems. Highlighted the need for opportunity to discuss body image and sexuality changes in open communication with health professionals.
Mansson *et al.* (1991)	Well reported	Poorly reported – limited information about interview procedure	Poorly reported – no details of analysis and no supporting quotes from participants	Swedish cohort. Patients interviewed after cystectomy to explore post-operative adjustment, psychological and emotional changes.	Majority of patients reported difficulty in post-operative period, with physical or psychological problems, and difficulty with stoma/collection bag. Sexual function had changed in many patients which some reported to have had a negative impact on their relationship. 14 patients reported negative change in mood. Self-esteem diminished in 7 patients.
Kressin *et al.* (2010)	Poorly reported (abstract only)	Poorly reported (abstract only)	Poorly reported (abstract only)	USA cohort. Women who had undergone cystectomy completed Sexual Function questionnaire	Conference poster abstract only. 7/14 (50%) were not sexually active, commonly due to low libido. Sexual function score corresponded to poor function. 85% received no sexual counselling prior to surgery. 71% (10/14) would have wanted to be counselled.
Dearing (2005)	Poorly reported – no details of respondents	Adequately reported	Adequately reported	UK cohort. Patients with non-muscle invasive bladder cancer having follow-up cystoscopy.	51% of patients were unaware of their diagnosis, having been informed they had 'warts' or 'bleeding areas' in the bladder. Of the 'ever' smokers, 12 (22%) were aware that smoking was a risk factor for the development of bladder cancer, and 7 (13%) were aware that continued smoking could worsen prognosis. 18 (33%) had been told to stop smoking, for any reason by their GP and 4 (7%) had been told to stop by urologist.
Ronaldson (2004)	Poorly reported – no details of respondents	Adequately reported	Adequately reported	UK cohort. Patients who had undergone cystectomy and ileal conduit diversion in the last 6 years	Mostly positive feedback regarding in-patient stays and pre-operative information. Stoma care nurse was highly praised. Several concerns were expressed related to difficulty with confidence, mood changes, living with urostomy and initial impact on their lives. Fear of leaking bags, dressing differently, restricted activities, depression and other concerns about follow-up and the fear of further cancer.
Faithful *et al.* (2001)	Well reported	Well reported	Well reported and rigorous analysis	UK cohort. Majority population were men undergoing radiotherapy for prostate cancer.	Symptom scores were similar between patients receiving nurse-led or conventional follow-up. Those who received nurse-led follow-up were

					significantly more satisfied and valued the continuity of care.

References to included studies

Dearing, J. Disease-centred advice for patients with superficial transitional cell carcinoma of the bladder. Annals of the Royal College of Surgeons of England 2005; 87(2): 85-87.

Faithfull, S et al. Evaluation of nurse-led follow up for patients undergoing pelvic radiotherapy. British Journal of Cancer 2001; 85(12): 1853-1864.

Fitch, MI et al. Radical cystectomy for bladder cancer: a qualitative study of patient experiences and implications for practice. Canadian Oncology Nursing Journal 2010; 20(4): 177-187.

Kressin, M. et al. Sexual function and demand for sexual counseling in women after radical cystectomy for bladder cancer. Journal of Sexual Medicine 2010; 7(Suppl. 3): 118-148.

Mansson, A et al. Psychosocial adjustment to cystectomy for bladder carcinoma and effects on interpersonal relationships. Scandinavian Journal of Caring Sciences 1991; 5(3): 129-134.

Ronaldson, S. Patient stories: the cystectomy experience. N2N: Nurse2Nurse 2004; 4(1): 21-22.

References to excluded studies (with reasons for exclusion)

Singh, JA et al. Preferred Roles in Treatment Decision Making Among Patients With Cancer: A Pooled Analysis of Studies Using the Control Preferences Scale. American Journal of Managed Care 2010; 16(9): 688-696.

Reason: not relevant to PICO (no CNS/key worker component)

Arora, NK et al. Assessment of quality of cancer-related follow-up care from the cancer survivor's perspective. Journal of Clinical Oncology 2011; 29(10): 1280-1289.

Reason: not relevant to PICO (no CNS/key worker component)

Skea, ZC. Enabling mutual helping? Examining variable needs for facilitated peer support. Patient Education and Counseling 2011; 85(2): e120-e125.

Reason: not relevant to PICO (no CNS/key worker component)

Arora, NK et al. Physicians' decision-making style and psychosocial outcomes among cancer survivors. Patient Education & Counseling 2009; 77(3): 404-412.

Reason: not relevant to PICO (no CNS/key worker component)

Bauer, C. Minimizing the mystery of bladder cancer surgery: Nursing interventions to decrease uncertainty in illness for patients undergoing cystectomy with a continent urinary diversion. Journal of Wound Ostomy and Continence Nursing 2007; 34(3): S39-S40.

Reason: abstract only, no data (protocol for study)

Allareddy, V et al. Quality of life in long-term survivors of bladder cancer. Cancer 2006; 106(11): 2355-2362.

Reason: not relevant to PICO no CNS/key worker component

Botteman, MF et al. Quality of life aspects of bladder cancer: a review of the literature. Quality of Life Research 2003; 12(6): 675-688.

Reason: not relevant to PICO

Matthews, SD and Courts, NF. Orthotopic neobladder surgery: nursing care promotes independence in patients with bladder cancer. American Journal of Nursing 2001; 101(7): 24AA-24AA, 24CC, 24EE.

Reason: expert review on stoma management

Sengelov, L et al. The functional and psychosocial status of patients with disseminated bladder cancer. Urologic Oncology 2000; 5(1): 20-24.

Reason: not relevant to PICO (no CNS/key worker component)

Jenks, JM. The influence of ostomy surgery on body image in patients with cancer. Applied nursing research 1997; 10(4): 174-180.

Reason: No CNS/key worker component, mostly bowel cancer

Erwin-Toth, P and Calabrese, DA. Nursing issues in the management of urinary diversions in women. Seminars in Urologic Oncology 1997; 15(3): 193-199.

Reason: expert review

Caffo, O et al. Assessment of quality of life after cystectomy or conservative therapy for patients with infiltrating bladder carcinoma - A survey by a self-administered questionnaire. Cancer 1996; 78(5): 1089-1097.

Reason: not relevant to PICO (no CNS/key worker component)

Switters, DM, Soares, SE, and White, RW. Nursing care of the patient receiving intravesical chemotherapy. Urologic Nursing 1992; 12(4): 136-139.

Reason: expert review

Fossa, SD et al. Life with an ileal conduit in cystectomized bladder cancer patients: expectations and experience. Scandinavian Journal of Urology & Nephrology 1987; 21(2): 97-101.

Reason: not relevant to PICO

Kurpad, R et al. A multidisciplinary approach to the management of urologic malignancies: Does it influence diagnostic and treatment decisions? Urologic Oncology-Seminars and Original Investigations 2011; 29(4): 378-382.

Reason: not relevant to PICO (no patient reported outcomes)

Smith, SG et al. Psychological impairment in patients urgently referred for prostate and bladder cancer investigations: the role of trait emotional intelligence and perceived social support. Supportive Care in Cancer 2012; 20(4): 699-704.

Reason: not relevant to PICO

El, Turabi. Variation in reported experience of involvement in cancer treatment decision making: Evidence from the National Cancer Patient Experience Survey. British Journal of Cancer 2013; 109(3): 780-787.

Reason: Not relevant to PICO - included in Topic A1

Ali, NS and Khalil, HZ. Effect of psychoeducational intervention on anxiety among Egyptian bladder cancer patients. Cancer Nursing 1989; 12(4): 236-242.

Reason: not generalisable to current UK population (all participants receiving pre-operative education were illiterate Egyptian patients with no formal education)

White, ID. Assessment of treatment-induced female sexual morbidity in oncology: Is this a part of routine medical follow-up after radical pelvic radiotherapy. British Journal of Cancer 2011; 105(7): 903-910.

Reason: no bladder cancer patients, no patient-reported outcomes

Henningsohn, L et al. Relative importance of sources of symptom-induced distress in urinary bladder cancer survivors. European Urology 2003; 43(6): 651-662.

Reason: no CNS/key worker component/ no information and support needs assessment

Furukawa, C et al. Health-related quality of life and its relevant factors in Japanese patients with a urostomy. Journal of Wound, Ostomy, & Continence Nursing 2013; 40(2): 165-170.

Reason: not relevant to PICO

Ong, K et al. Orthotopic bladder substitution (neobladder): part I: indications, patient selection, preoperative education, and counseling. Journal of Wound, Ostomy, & Continence Nursing 2013; 40(1): 73-82.

Reason: not relevant to PICO

Mclnnes, DK. Perceptions of cancer-related information among cancer survivors a report from the American Cancer Society's studies of cancer survivors. Cancer 2008; 113(6): 1471-1479.

Reason: no CNS/key worker component

Evidence tables

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of participants</th><th>Participant characteristics</th><th>Methods</th><th>Outcome measures</th><th>Additional comments</th></tr>
<tr>
<td>Fitch 2010

Canada</td>
<td>Qualitative interview study</td>
<td>22 who had undergone cystectomy for bladder cancer</td>
<td>
<table>
<tr><th></th><th>Men (n=13)</th><th>Women (n=9)</th></tr>
<tr><td>Mean age</td><td>68.4</td><td>73.1</td></tr>
<tr><td>Age range</td><td>44-82</td><td>58-85</td></tr>
<tr><td>Married</td><td>10</td><td>2</td></tr>
<tr><td>Widowed</td><td>0</td><td>3</td></tr>
<tr><td>Divorced</td><td>2</td><td>3</td></tr>
<tr><td>single</td><td>1</td><td>1</td></tr>
<tr><td>Ileal conduit</td><td>5</td><td>4</td></tr>
<tr><td>Neobladder</td><td>9</td><td>4</td></tr>
<tr><td>NB converted to IC</td><td>0</td><td>1</td></tr>
</table>
</td>
<td>In depth interview 12-36 months after surgery to explore participants experiences and perceptions about 1) diagnosis, 2) surgery, 3) living with changes following surgery
Focus group held for participants to attend where the preliminary analysis was presented. This allowed opportunity for additional input by participants and reaction to analysis. Content and theme identification used to analyse the transcripts.</td>
<td>Themes identified:
1) Lack of knowledge of bladder cancer (causes, risk factors, symptoms)
2) Feeling shock and fear at diagnosis (some felt loss of control others were more accepting)
3) Desire for open communication with health professionals – they wanted information about bladder cancer and treatment plans to be clear, consistent, in a timely fashion to avoid anxiety and confusion.
4) Desire for information – additional information or to speak to others who had bladder cancer or urinary diversion was important for most participants. Helpful if family or friends were present when receiving information from health care providers
5) Importance of support of family and friends – for many there were new experiences to face and need to learn new techniques, e.g. toileting, catheterisation, appliance changes.
6) Initial recovery period – overall hospital care was perceived to be good. Homecare was more varied and depended where the person lived, knowledge of nursing staff about surgical procedure and availability of family and friends.
7) Dealing with incontinence – incontinence or leakage from pouch was frustrating and challenging. Many had not received instruction about what to do and health care professionals in the community did not have the necessary knowledge for these post-operative challenges.
8) Adjusting to body image and function – more pronounced for participants with an ileal conduit or who were younger. Some accepted changes, others described having to work to find ways to live with the changes as best they could.
9) Alterations in sexual relationships – influenced by age and their perceived stage of life, the type of surgery and</td>
<td>Well designed, clear methodology and robust analysis.</td>
</tr>
</table>

					the changes in actual functioning, how much importance placed on sexual relationship and whether there was a long-term relationship. Participants described the value of intimacy and how it continued and improved through the cancer experience. **10) Changes in life perspectives** – many felt their lives would never be the same again, and needed to find as much normality as possible, many realised their priorities had changed and perspectives about what was important had been altered. From focus groups participants needed more post-operative information about what to expect – in particular they wanted info about diet progression, care of scars, infections, homecare, follow-up care plans, cancer surveillance. This needed to be distributed in a variety of ways e.g. posters, books, awareness campaigns and education packages for patients. In addition, open communication with health care providers is essential, particularly the opportunity to have questions answered and to have issues and concerns explored as they relate to specific body image and sexuality changes.	
Mansson 1991 Sweden	Qualitative interview study	34 patients who had cystectomy for bladder cancer 1-10 (mean 5) yrs ago and were free from malignancy	28 men, 6 women. Mean age 60 (range 46-79). 20 patients had ileal or colonic conduit diversion, 14 had continent caecal reservoir.	Semi-structured interview to explore experience of cancer, preoperatively received information, relations with health services, interpersonal experiences, postoperative adjustment and psychological and emotional changes	**Themes identified:** **1) Pre-operative information** – all patients considered to have adequate information about bladder cancer, cystectomy and urinary diversion. 25 patients reported a crisis like response such as feelings of isolation and fear. 11 patients reported that the impact on sexual function was inadequately discussed before surgery. 3 patients said they had received no information at all on sexual changes. **2) Pre and post-operative adjustment and relations to health-care providers** – 10 patients described a feeling of relief when admitted for treatment, 9 reported fear, 15 could not recall any specific reaction. 30/34 patients reported that they could approach hospital staff with any questions regarding their disease. The post-operative months were reported as difficult by 23 patients. Only 4 patients reported support had been received from hospital staff during this period. 12 patients complained of physical problems related to stoma, 11 had psychological or mental	Methods and analysis not well reported. Surgery techniques, information and support services may have changed since study was conducted. Not UK population.

					problems. 10 felt they had no one to counsel them. 15 expressed fear of recurrence. **3) Stoma, sexual function and co-habitation** – 14 reported constant awareness of the soma/collecting bag, and was experienced as disturbing by 10. 25 patients reported difficult situations due to stoma/bag. Common negative consequences concerned sexual function, which had changed in all 30 patients with partners, but libido had only diminished in 16. Erectile dysfunction in 6/28 men. Relations with partner had been negatively influenced by the urostomy and sexual problems in 13 cases. 32/34 stated that their operation had not influenced their relationship with other people. **4) Mood and emotions** – 14 people reported change in mood, who felt more irritable, gloomier, more sensitive, more nervous or more easily moved. 20 reported that their outlook on life had changed after surgery – increased tolerance, patience and gratitude. Self-esteem diminished in 7 patients, commonly due to fatigue, sexual problems, and changed body image. 31 patients could accept their affliction with a malignant disease, only 23 could accept their present situation. These psychological and emotional problems were equally common in patients with conduit and those with reservoir.	
Kressin 2010 USA	Cross-sectional questionnaire	14 women after cystectomy for bladder cancer	Not reported	Surveys consisting of the Female Sexual Functioning Index (FSFI) were completed by 14 respondents	7/14 (50%) were not sexually active, commonly due to low libido. Average FSFI score = 15.9 corresponding to poor function. 85% received no sexual counselling prior to surgery. 71% (10/14) would have wanted to be counselled	Conference poster abstract only. Response rate unknown.
Dearing 2005 UK	Cross-sectional questionnaire	78 patients attending for follow-up flexible cystoscopy after diagnosis of pTa or pT1 TCC at a DGH over 3-	Not reported	Patients completed questionnaire documenting awareness of underlying diagnosis, smoking status, awareness of smoking as a risk factor for development of their disease. A nurse was available to assist patients and answer any queries. A notional gold	71% (55/78) had been smokers at some time, 24 (31%) continued to smoke at the time of follow-up. 26 of those 55 (47%) were aware of their underlying diagnosis, with those ignorant of their condition having been informed only that they had 'warts' or 'bleeding areas' in the bladder. In non-smokers 12 (52%) were aware of their disease. Of the 'ever' smokers, only 12 (22%) were aware that	

		month period		standard of information provision was that all patients would have been told their exact diagnosis, the linkage between smoking and their disease and would have been advised to stop and would have done so.	smoking was a risk factor for the development of bladder cancer, and 7 (13%) were aware that continued smoking could worsen prognosis. 18 (33%) of the smoking patients had been told to stop smoking, for any reason by their GP and 4 (7%) had been told to stop by urologist. Recurrence in ever smokers was 53% and 52% in never smokers.	
Ronaldson 2004 UK	Qualitative study	6 patients who had cystectomy and ileal conduit formation in the previous 6 years. Patients were randomly selected from database – respective consultants were asked to verify that each patient was alive and well. All participants treated by same consultant.	Not reported	'Patient stories' method. Patients interviewed about their experience of cancer, starting with symptoms and presentation to GP. Active listening and non-directive prompts were used to encourage patient to talk. Conversations were 'mapped' using Buzan's mind mapping process. The completed map enables thoughts and ideas to be linked together along any number of events to a central experience, allowing important issues to be identified. A Macmillan Lung Specialist Nurse - who worked independently of the urology department - conducted the interviews to ensure anonymity and confidentiality. All participants chose to be interviewed in their own homes.	Common themes from all 6 interviews were identified and points for action were drawn up: **Delayed referral:** majority of patients seen in the one stop haematuria clinic within a fortnight of referral from GP. **In-patient stay:** Mostly positive feedback was given. One man reported being reluctant to ask for help to move in bed because the staff were so busy. **Information regarding test results:** Feelings of anxiety were reported when it came to receiving test results and felt that the policy used by the department of 'no news is good news' was not satisfactory. **Bowel preparation:** Pre-operative rectal washouts were considered to be 'embarrassing' and 'undignified'. It was then agreed that these were no longer necessary. A regime of 2 consecutive days of bowel cleansing solution, IV fluids and a low residue diet was retained. **Confidence and living with a urostomy:** Most patients commented that the information they had been given before the operation was excellent. The district nurses were acknowledged by all and GP support mentioned by most. The stoma care nurse was praised for kindness and prompt service provided. Several concerns were expressed related to difficulty with confidence, mood changes, living with urostomy and initial impact on their lives. Fear of leaking bags, dressing differently, restricted activities, depression and other concerns about follow-up and the fear of hearing that the cancer had come back.	Patient stories project to enable service change. Patient story technique adopted from RCN Leadership Development Program.
Faithful	Randomised	115 men receiving radical	Median age 70 (range 49-83)	Patients randomised to conventional care or care from	Mean 1.6 hours consultation time per patient over the 12	94% of satisfaction

2001 UK	trial 1995-1997	radiotherapy for prostate or bladder cancer	95 (83%) prostate cancer, 20 (17%) bladder cancer. 78% 60-64 Gy radiation dose	a clinical nurse specialist. Satisfaction with care was evaluated using a self-assessment questionnaire 12wks after start of RT. Nurse-led care was established at start of therapy and throughout treatment. Nurse provided information and answered patients' questions. Leaflets on healthy eating, managing urinary symptoms during RT. Telephone contact maintained to assess health status between clinics. The provision of information and practical advice on how to recognise early symptoms, what to expect from treatment and how to manage existing problems. Conventional care consisted of routine medical appointments lasting 10mins within the urology outpatient setting during treatment.	weeks of study for both groups. **Satisfaction** Men were overall very content with clinical care in both groups. Intervention group were significantly more satisfied with their follow-up care than men in the control group. Nurse-led clinic perceived as providing a greater about of information: 91% of men in the intervention group were positive about this aspect compared to 82% in the control group. All patients rated the RT treatment very positively but in the control group 23% commented on the lack of continuity in follow-up care. Men in the intervention group felt well informed, felt their concerns were taken seriously, liked the continuity and the fact that their families were included in the consultation. **Quality of life** Quality of life (measured with EORTC QLQ-C30) assessments at weeks 6 and 12 showed few differences between intervention and control groups. Functional scores were high overall, with some evidence of significant difference between intervention and control groups in physical functioning at 12 weeks, suggesting those in the intervention arm were less physically impaired. Higher levels of constipation were seen at this point in the control group compared with the intervention group.	questionnaires were returned. 81% of the EORTC quality of life questionnaires completed.

1.3 Specialist palliative care needs at end of life

Review question: Which elements of specialist palliative care services are most important for bladder cancer patients and/or their carers during end-of-life care?

Rationale

Bladder cancer patients nearing end-of-life and their carers may have specific information and support needs. This review questions aims to explore the most important aspects of palliative care services for these patients.

Question in PICO format

Sample	Phenomenon of interest	Evaluation
Patients with bladder cancer (& their carers) who are candidates for palliative care	Palliative care specialists during end-of-life care	• Patient (and carer) satisfaction (with communication, information, support and treatment received) • Health-related quality of life (inc. patient and carer-reported outcomes) • Understanding/knowledge of disease and treatment • Psychological factors (e.g. distress, coping) • Perceived social support • Informed choice and decision-making • Ability to self-manage condition/side-effects • Referral to support groups/networks

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

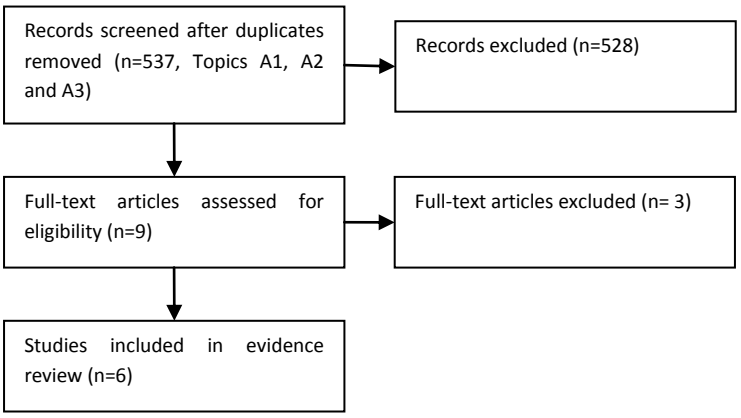
Data synthesis

Evidence from cross-sectional questionnaire studies was appraised using relevant criteria from the NICE methodology checklist for qualitative studies. A narrative summary of the evidence was presented.

RESULTS

Result of the literature searches

Figure 3. Study flow diagram



Study quality and results

Six studies were identified, including one systematic review and five cross-sectional questionnaire studies. Details of the included studies are summarised in Table 4.

Evidence statements

In three studies, the respondents were carers of cancer patients who had received palliative care. The study by Fakhoury *et al.* (1997) reports carer's satisfaction with community nurses, hospital doctors and GPs, but does not specify that patients were treated within a specialist palliative care team. Most carers were highly satisfied with the different providers, but the least satisfaction was reported by those who cared for patients with genito-urinary tumours. Duration of pain was not related to any of the satisfaction measures. Teunissen *et al.* (2006) reported that the main support needs in palliative care for all ages was the need for functional support and support in coping. Older patients (aged 70 or over) reported less need for relational support or support in communication than younger respondents. A Swedish study of women who had lost their husband/partner to prostate or bladder cancer reported that 93% of patients had adequate access to pain control during the last 3 months of life, whereas only 33% had access to psychological support. The cancer patient's mental health status at the end-of-life was also predictive of the widows' anxiety and depression at follow-up (Valdimarsdottir *et al.*, 2002).

In a Japanese study, bereaved family members of cancer patients rated that 25% of patients experienced a mild self-perceived burden, and 25% experienced moderate to severe self-perceived burden. Family members rated care strategies to alleviate patient-perceived burden, the most useful being 1) eliminating pain and other symptoms that restrict patient activity; 2) quickly disposing of urine and stools so that they are out of sight; 3) supporting patients' efforts to care for themselves (Akazawa *et al.*, 2010). One systematic review aimed to explore self-care strategies in end-of-life care in advanced cancer (Johnston *et al.*, 2009). Although self- care strategies such as using information and using distraction techniques were identified these were largely initiated by researchers. No research used a patient-centred approach and the author concluded that self-care in advanced cancer is an under-explored area. Factors that prevented patients to self-care were low education, poor socio-economic status, psychological distress and physical limitations.

One study of a UK urology ward's inpatients and outpatients with advanced or metastatic urological cancer reported that 75% of out-patients had specific problems or were generally unwell as a result of their disease and would have benefitted from specialist palliative care. 25% were well at the time

of their visit but potential psychosocial problems arising from coping with terminal disease were not addressed (Brierly & O'Brien, 2008).

Table 4. Summary of included studies

Study	Population	Methods	Analysis	Relevance to guideline population	Key findings
Fakhoury *et al.* (1997)	Well reported	Well reported	Well reported but limited outcomes	UK population. Carers of patients with various primary cancers. Does not specify care by specialist palliative care team.	Over 70% of carers were satisfied with health professionals. Duration of patient pain was not associated with satisfaction. Patients' cognitive and psychological functioning associated with carer's satisfaction.
Teunissen *et al.* (2006)	Well reported	Poorly reported	Well reported	Dutch population. Patients with various primary cancers referred to palliative care team	The main support needs for all age groups were the need for functional support and support in coping. Less need for relational support and support in communication with advancing age.
Valdimars -dottir *et al.* (2002)	Well reported	Well reported. Standardised measures used but questionnaires completed 2-4 years after death of spouse.	Well reported	Swedish population. Women whose husbands/partners had died from bladder or prostate cancer.	93% reported having access to pain control during last 3mo of life compared to 33% having access to psychological support.
Akazawa *et al.* (2010)	Poorly reported	Well reported	Well reported	Japanese population. Primary tumour site not stated. Respondents were bereaved family members as part of the Japan Hospice and Palliative Care Evaluation.	25% reported patient having moderate to severe self-perceived burden. Useful strategies to reduce burden 'Eliminate pain and other symptoms', 'Quickly dispose of urine and stools', 'Support patients to care for themselves'
Johnston *et al.* (2009) (review)	Well reported	Well reported	Well reported narrative summary of evidence	Review of self-care at end-of-life in advanced cancer. Concluded that evidence in this area is limited.	Self care strategies should be related to helping patients cope with pain and debilitating symptoms, coping emotionally and adjusting psychologically to their illness and alleviating distress associated with symptoms that cannot easily be improved e.g. weight loss.
Brierly & O'Brien (2008)	Well reported	Well reported	Poorly reported	UK population of urology inpatients and outpatients.	Many urological cancer patients were well at admission but important psychosocial issues were often not addressed during consultation

References to included studies

Akazawa, T. et al. Self-Perceived Burden in Terminally Ill Cancer Patients: A Categorization of Care Strategies Based on Bereaved Family Members' Perspectives. Journal of Pain and Symptom Management 2010; 40(2): 224-234.

Brierly, R.D. and O'Brien, T.S. The importance of palliative care in urology. Urologia Internationalis 2008; 80(1): 13-18.

Fakhoury, W.K. et al. The effects of the clinical characteristics of dying cancer patients on informal caregivers' satisfaction with palliative care. Palliative Medicine 1997; 11(2): 107-115.

Johnston, B. et al. Self care and end of life care in advanced cancer: literature review. European Journal of Oncology Nursing 2009; 13(5): 386-398.

Teunissen, S.C. et al. Does age matter in palliative care? Critical Reviews in Oncology Hematology 2006; 60(2): 152-158.

Valdimarsdottir, U et al. The unrecognised cost of cancer patients' unrelieved symptoms: a nationwide follow-up of their surviving partners. British Journal of Cancer 2002; 86(10): 1540-1545.

References to excluded studies (with reasons for exclusion)

Aubin, M et al. Interventions to improve continuity of care in the follow-up of patients with cancer. Cochrane.Database.of Systematic.Reviews. 2012;(7)

Reason: not relevant to PICO

Mayland, CR. Does the 'Liverpool Care Pathway' facilitate an improvement in quality of care for dying cancer patients. British Journal of Cancer 2013; 108(10): 1942-1948.

Reason: Liverpool care pathway being phased out

Ylitalo, N et al. Guilt after the loss of a husband to cancer: Is there a relation with the health care provided? Acta Oncologica 2008; 47(5): 870-878.

Reason: not relevant to palliative care

Evidence tables

Study, country	Study type, study period	Number of participants	Participant characteristics		Methods	Outcome measures	Additional comments
Fakhoury 1997 UK	Retrospective interview study 1990	1858 informal caregivers of people who died from cancer in 1990 (ICD codes 140-208)	Age of patient	N (%)	Data collected for the Regional Study of Care of the Dying (RSCD) – retrospective survey of family members of people who died in 20 health districts in England about 10 mo after patient's death. Interview covered nursing, medical and social services, support and bereavement services for carers.	Satisfaction with community nurses, GPs, hospital doctors. Excellent or good ratings of services CNs 87%; GPs 71%; hospital doctors 77% No association between age of patient, sex of carer and carer's satisfaction. Carers who were 65+ were more likely to be highly satisfied with services from GPs (45%) and hospital doctors (39%). If carer was spouse or partner associated with high satisfaction with all providers. Site of cancer: 50% of genito-urinary tumours rated high satisfaction with CNs, 37% with GPs, 30% high with hospital doctors. GU cancer carers less likely to report high satisfaction with hospital doctors. Duration of patient pain was not associated with satisfaction. Carers who perceived that the patient experience cognitive and psychological functioning symptoms for a short time compared to a long time reported higher satisfaction with the different providers. Patients who were functionally limited for a short period of time were more likely to report high satisfaction with hospital doctors and low satisfaction with GPs.	Doesn't specify care by MDT or specialist palliative care team.
			<55	198 (10.7)			
			55-64	307 (16.5)			
			65-74	523 (28.1)			
			75-84	609 (32.8)			
			85+	221 (11.9)			
			Male	961 (51.7)			
			Female	897 (48.3)			
			Site of cancer				
			Digestive organs/peritoneum	508 (27.3)			
			Respiratory	420 (22.6)			
			Bone/breast/skin	228 (12.3)			
			Genito-urinary	297 (16)			
			Lymphatic	138 (7.4)			
			Other	267 (14)			
			Place of death				
			Home	571 (30.7)			
			Hospital	937 (50.4)			
			Hospice	257 (13.8)			
			Nursing home	93 (5)			
			Age of carer				
			<55	752 (40.5)			
			55-64	447 (24.1)			
			65-74	402 (21.6)			
			75+	257 (13.8)			
			Male	626 (33.7)			
			Female	1232 (66.3)			
			Relationship to patient				
			Spouse/partner	868 (46.7)			
			Child/child-in-law	590 (31.8)			
			Relative	292 (15.7)			
			Close friend/neighbour	108 (5.8)			

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of participants</th><th>Participant characteristics</th><th>Methods</th><th>Outcome measures</th><th>Additional comments</th></tr>
<tr>
<td>Teunissen 2006

Netherlands</td>
<td>Prospective observational study

1998-2004</td>
<td>181 patients referred to the Palliative Care Team of Dept Medical Oncology</td>
<td>
<table>
<tr><td></td><td></td></tr>
<tr><td></td><td>N(%)</td></tr>
<tr><td><60 yr</td><td>56%</td></tr>
<tr><td>60-70y</td><td>21%</td></tr>
<tr><td>≥70y</td><td>23%</td></tr>
<tr><td>>85y</td><td>(3%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Primary cancer</td><td></td></tr>
<tr><td>breast</td><td>25 (13%)</td></tr>
<tr><td>Gynae</td><td>21 (12%)</td></tr>
<tr><td>GI</td><td>35 (19%)</td></tr>
<tr><td>Head&neck</td><td>21 (12%)</td></tr>
<tr><td>lung</td><td>20 (11%)</td></tr>
<tr><td>prostate</td><td>13 (7%)</td></tr>
<tr><td>other</td><td>46 (25%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
</table>
</td>
<td>Symptoms, problems, and needs were assessed as dichotomous variables by means of an interview of the patient by the clinical nurse specialist of the PCT using a standardised list. Palliative care problems were defined as spiritual, emotional, social and functional issues requiring professional assistance. Actual wishes to receive professional support in these domains were labelled as palliative needs.</td>
<td>
<table>
<tr><td><60y</td><td>60-70y</td><td>≥70y</td></tr>
<tr><td colspan="3">Functional support needs</td></tr>
<tr><td>60 (58%)</td><td>29 (76%)</td><td>24 (60%)</td></tr>
<tr><td colspan="3">Support in coping</td></tr>
<tr><td>65 (63%)</td><td>23 (61%)</td><td>16 (40%)</td></tr>
<tr><td colspan="3">Emotional support</td></tr>
<tr><td>35 (34%)</td><td>11 (29%)</td><td>14 (35%)</td></tr>
<tr><td colspan="3">Support of informal caregivers</td></tr>
<tr><td>40 (39%)</td><td>11(29%)</td><td>11 (28%)</td></tr>
<tr><td colspan="3">Spiritual support</td></tr>
<tr><td>8 (8%)</td><td>1 (3%)</td><td>5 (13%)</td></tr>
<tr><td colspan="3">Co-ordination of care</td></tr>
<tr><td>6 (6%)</td><td>8 (21%)</td><td>4 (10%)</td></tr>
<tr><td colspan="3">Relational support</td></tr>
<tr><td>14 (14%)</td><td>3 (8%)</td><td>1 (3%)</td></tr>
<tr><td colspan="3">Support in communication</td></tr>
<tr><td>11 (11%)</td><td>3 (8%)</td><td>0 (0%)</td></tr>
<tr><td colspan="3">Median no. of needs for support</td></tr>
<tr><td>2</td><td>2</td><td>2</td></tr>
</table>

8 unmet support needs occurred in ≥10% in at least one of the age groups. The main support needs for all age groups were the need for functional support, in particular the middle-aged group, and support in coping, predominantly in the younger and middle aged group. Less need of relational support and support in communication with advancing age.
</td>
<td>Not reported number of bladder or urological cancer patients.</td>
</tr>
<tr>
<td>Valdimarsdottir 2002

Sweden</td>
<td>Questionnaire study

1999</td>
<td>379 women <80y who lost their husband/partner to prostate or bladder cancer</td>
<td>Average of 3 years elapsed between death of patient and follow-up time point.

<table>
<tr><td></td><td>N (%)</td></tr>
<tr><td>50-59 y</td><td>48 (13)</td></tr>
<tr><td>60-69y</td><td>154 (41)</td></tr>
<tr><td>70-79y</td><td>167 (44)</td></tr>
<tr><td>single</td><td>345 (91)</td></tr>
<tr><td>married</td><td>7 (2)</td></tr>
</table>
</td>
<td>Anonymous postal questionnaire completed 2-4 years after their loss.
Questions asked widow to report patients' distress, pain, depression and anxiety during last 3 months of life. Access to pain control and psychological support. Widow asked to report on her</td>
<td>Widows reports on patients access to pain control and psychological support:

6/364 (2%) no need for pain control; 51/337 (15%) no need for psych support. 93% had moderate or much access to pain control during last 3mo of life compared to 33% regarding psychological support.</td>
<td></td>
</tr>
</table>

Study, country	Study type, study period	Number of participants	Participant characteristics	Methods	Outcome measures	Additional comments
				own psychological well being and quality of life. State-trait anxiety inventory and CES-D measure of depression.	66% of patients were assessed as to have been moderately or much depressed during last 3 mo, 62% as anxious, and 87% as in pain. Patients' mental health status during last 3 mo was predictive of widow's anxiety and depression at follow-up.	
Akazawa 2010 Japan	Cross-sectional survey 2007	469 bereaved families of cancer patients who had died at one of 153 certified palliative care units.	Patient: N (%) Mean age: 71 Male: 241 (57) Female: 184 (43) Family member: Mean age: 58 Male: 125 (30) Female: 298 (70) Relationship with patient: Spouse: 191 (45) Son/daughter: 162 (38) Son/daughter in law: 29 (7) Sibling: 23 (5) Parent: 7 (2) Other: 13 (3) Interval from patient death: Mean months: 13 Time with patient in final week: Every day: 280 (65) 4-6 days: 56 (13) 1-3 days: 74 (17) None: 14 (3)	Cross sectional anonymous survey Including Care Evaluation Scale and death experience scale, and 12 additional questionnaires for assessing further factors – to assess the patients perceived burden from the bereaved family members' perspective and to evaluate care strategies that alleviate the sense of burden.	429 responses were analysed. **Prevalence of self-perceived burden rated by family member**: 109 (25%) mild burden, 68 (16%) moderate, and 38 (9%) severe self-perceived burden. **Usefulness of care strategies for reducing burden rated by 40% or more of respondents as very useful:** Eliminate pain and other symptoms that restrict patient activity (53%); Quickly dispose of urine and stools so that they are out of sight (52%); Support patients to care for themselves (45%); Present a variety of alternatives for daily life from which the patient may choose (45%); Ask 'is there anything I can do for you?' (Not 'what do you need me to do?') (42%); Factor analysis presented7 interpretable factors. 1) offer different perspectives, 2) assist patients with their daily life activities in a natural manner, 3) strengthen the sense that the patients' value is intact, 4) avoid condescending attitude, 5) facilitate communication between patient and family, 6) support patients efforts to care for themselves, 7) minimise patient disability.	Primary cancer site of patient not reported.

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of participants</th><th>Participant characteristics</th><th>Methods</th><th>Outcome measures</th><th>Additional comments</th></tr>
<tr>
<td>Johnston 2009

UK</td>
<td>Review of self care and end of life care in advancer cancer

18 papers published 1996-2008</td>
<td>n/a</td>
<td>n/a</td>
<td>Review aim was to find out what self care strategies enable patients and carers to engage with their end of life care and how can self care in advanced cancer be improved.</td>
<td>Three main themes from literature review

<table>
<tr><td>Interventions for end of life care</td><td>Education programmes and symptom focused interventions</td></tr>
<tr><td>Self care behaviours used by patient</td><td>Social support
Symptom improvement
Taking medication
Information
Using creative activity
CAM</td></tr>
<tr><td>Factors that prevent patients to self care</td><td>Low education
Poor socio-economic status
Psychological distress
Physical limitations/ symptom burden</td></tr>
</table>

Concluded that it is difficult to reach firm conclusions about how people manage their illness themselves with advanced cancer at end of life – underdeveloped and under researched area. Although self care strategies such as using information and using distraction techniques were identified these were largely initiated by researchers. No research used a patient centred approach. Self care strategies should be related to helping them cope with pain and debilitating symptoms, coping emotionally and adjusting psychologically to their illness and alleviating distress associated with symptoms that</td>
<td></td>
</tr>
</table>

Study, country	Study type, study period	Number of participants	Participant characteristics	Methods	Outcome measures	Additional comments
					cannot easily be improved e.g. weight loss.	
Brierly (2008) UK	Observational study Study period not reported	881 urology ward admissions during a 4-month period were reviewed. 24 patients with terminal malignancy who had 27 in-patient admissions. 795 outpatient visits by patients with urological malignancy, and 82 visits with advanced malignancy	Patients had either unresectable or locally advanced disease or distant metastatic disease from the genitourinary tract. Average age =73.9 years (range 43-92). Average length of stay 16.6 days (range 1-36).	All admissions to the Urology Ward at Guy's Hospital were reviewed prospectively over a 4-month period. All patients with a diagnosis of advanced malignancy were identified and followed through the course of their admission. All urology out-patient visits were examined retrospectively be reviewing all clinic letters and identifying patients who were seen with advanced malignancy.	*In-patients (n=27, 11 bladder cancer)*: haematuria was the reason for admission in 8 patients. A member of hospital palliative care team visited all the patients, at least once during their admission, and this was usually the nurse specialist. *Out-patients (82advanced malignancy, 10 with bladder cancer, 795 cancer diagnosis, 127 bladder cancer)* For patients with advanced bladder or kidney cancer 30% were well at the time of their visit. 45% were in the terminal phase of their disease and were receiving palliative care or hospice support at home. However, it was noted that there may have been some important psychosocial issues with these patients, and this was not addressed during consultation. Three patients in this study were admitted with generalised symptoms of advancing malignant disease and 1 patient died from renal failure within 24h of admission. The authors suggest that these patients would have been managed more appropriately under the palliative care team, of if admitted directly to a hospice.	

1.4 Smoking cessation and long term outcomes for people with bladder cancer

Review question: Does smoking cessation affect outcomes for patients with bladder cancer?

Rationale

Research shows that, compared to non-smokers, smokers have approximately three times the risk of developing bladder cancer. People who stop smoking reduce their risk of developing bladder cancer by 30-60% within four years.

Consultant urologists and nurses who work with patients with bladder cancer routinely ask patients about their smoking history when they first attend for assessment of their symptoms.

Time of diagnosis would seem to be an ideal opportunity for motivating patients to stop smoking. However many health professionals are uncomfortable giving smoking cessation advice at this point, due to this time being one the key points in the patient pathway where increased psychological support is needed and patients often cite anxiety and stress as reasons for continued smoking or restarting smoking. As a result health professionals are uncertain when the best time is to give smoking cessation advice that will result in patients stopping smoking for the rest of their lives.

Although there is a large body of evidence which demonstrates the general health benefits on the heart and lungs of stopping smoking, some health professionals believe that smoking cessation advice given to patients diagnosed with bladder cancer would be more effective if specific reduction in risk of bladder cancer recurrence or progression rates could be demonstrated.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with diagnosed bladder cancer who have a smoking history	Smoking cessation	Smoking continued	• Recurrence rate • Overall survival • Disease-specific survival • Disease progression • Treatment-related morbidity • Health-related quality of life (inc. patient reported outcomes)

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in

the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

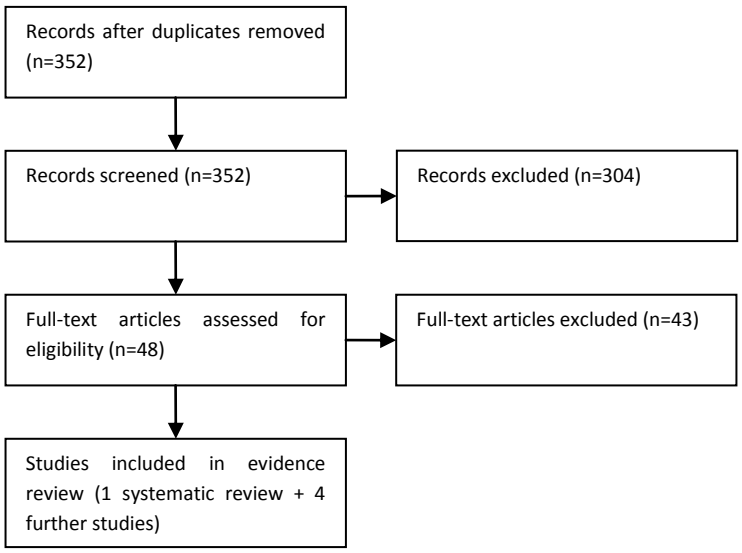
Data synthesis

Included studies were appraised using the NICE methodology checklist for systematic reviews and the checklist for prognostic studies. A narrative summary of the evidence was presented. Data was not pooled in the published systematic review due to heterogeneity across studies in classification of smoking status and patient characteristics (e.g. stage and grade of cancer). The smoking status of participants was important for this topic and data is presented accordingly (e.g. ex-smoker, current smoker, and time since smoking cessation). The timing of smoking cessation (e.g. before diagnosis, during treatment) was also included if reported.

RESULTS

Result of the literature searches

Figure 4. Study flow diagram



Study quality and results

One systematic review (Crivelli *et al.*, 2014) and a further three prognostic studies (Kim *et al.*, 2014; Wyszynski *et al.*, 2014; Wang *et al.*, 2014) were identified for the outcomes of recurrence, progression, cancer-specific survival, overall survival and treatment-related morbidity. One study presenting baseline data from a randomised trial (Ditre *et al.,* 2011) was identified for the outcome of health-related quality of life. The systematic review was clearly focused and relevant to the review question for this topic. However, many of the included studies focused on the impact of patients' smoking status on clinical outcomes rather than the effect of smoking cessation. The literature search was judged to be sufficiently rigorous and the methodology was well reported. No formal study quality assessment was reported in the systematic review. However, the studies were limited by heterogeneity in patient characteristics (i.e. stage and grade), follow-up time, and the categorization of smoking status, which precluded a meta-analysis. The use of intravesical therapy and repeat TURBT also varied across studies and was often not reported. The study by Ditre *et al.*

(2011) was considered to be of low quality because the population was not relevant to the review question (the majority of participants had lung or breast cancer). Study quality for the three further prognostic studies was assessed using the NICE methodology checklist for prognostic studies. The quality assessment item regarding loss to follow-up was not considered relevant to this review question. The outcome of the quality assessment is provided in Table 5. In all studies the study sample was clearly defined and represented the population of interest. All studies used an appropriate method of analysis and hazard ratios (HRs) were provided.

Table 5. Quality assessment of prognostic studies

Study	Quality criteria					Quality score
	1. Sample represents the population of interest?	**2. Prognostic factor adequately measured?**	**3. Outcome adequately measured?**	**4. Confounders accounted for?**	**5. Appropriate statistical analysis used?**	
Kim *et al.* (2014)	Yes	Yes	Yes	Yes	Yes	5/5
Wyszynski *et al.* (2014)	Yes	Unclear	Yes	Yes	Yes	4/5
Wang *et al.* (2014)	Yes	Yes	Yes	Yes	Yes	5/5

Narrative summary of evidence

Patients treated with TURBT: Recurrence, progression and survival

Hazard Ratios (HRs) for outcomes by category of smoking status for patients treated with TURBT are provided in Table 6. Nine out of 13 studies of patients treated with TURBT found a statistically significant association of smoking with disease recurrence. Two out of eight studies and two out of two studies, when stratified by smoking status and smoking exposure, respectively, found statistically significant associations between smoking and disease progression for patients treated with TURBT. The only study that evaluated the influence of smoking on disease-specific survival revealed no association. Overall survival was reported by four studies, all of which showed no significant associations with smoking, except for one study, which reported that continued smoking after diagnosis, but not former smoking, was associated with shorter overall survival compared to never smoking (Wyszynski *et al.,* 2014)

Impact of smoking cessation

One study reported significantly shorter recurrence-free survival (RFS) for those who continued to smoke after diagnosis compared to ex-smokers (HR 1.40, 95% CI 1.03-1.91), but similar RFS for ex-smokers who quit more than one year before diagnosis compared to those who quit within one year before and three months after diagnosis. Consistent with this finding, another study reported that patients who quit smoking ≥15 and <15 years before diagnosis (without excluding current smokers) did not differ with respect to RFS. One study reported no associations of smoking cessation with recurrence, progression, disease-specific mortality or overall mortality when categorised by cessation >10 years before diagnosis, 0.1-10 years before diagnosis, and at diagnosis. In one study, continued smokers were found to have a 2.2-fold increased risk of recurrence compared to

individuals who quit smoking within one year before and three months after diagnosis (HR 2.2, 95% CI 1.2-4.0), but patients who quit >1 year before diagnosis did not.

In an analysis of 1,549 individuals who had ever smoked, patients who quit smoking ≥10 years prior to TURBT had a lower risk of recurrence (HR 0.66, 95% CI 0.52-0.84) and progression (HR 0.42, 95% CI 0.22-0.83), but not overall survival when compared to current smokers. Similarly in one study which included only patients with recurrent NMIBC, those who quit smoking ≥10 years before TURBT had a 0.4 times (95% CI 0.23-0.67) lower risk of recurrence but not of disease progression than current smokers. Patients who quit smoking <10 years before TURBT did not have a reduced risk of disease recurrence or disease progression relative to current smokers.

Patients treated with radical cystectomy: Recurrence, progression and survival

Hazard Ratios (HRs) for outcomes by category of smoking status for patients treated with cystectomy are provided in Table 7. Three out of seven studies of patients treated with radical cystectomy found statistically significant associations of smoking with recurrence. The same studies also found that smoking was associated with disease-specific survival. Only one out of four studies found an association between smoking and overall survival, with smoking history being an independent prognostic factor for overall survival (HR 1.31, 95% CI 1.05-1.63). However, no distinction was made between former or current smokers.

Impact of smoking cessation

Four studies evaluated the associations between smoking cessation and outcomes of patients treated with radical cystectomy (n=2835). One study found that quitting smoking >10.1, 5.1-10, 1.1-5 and 0.1-1 year prior to diagnosis did not affect disease recurrence or disease-specific survival when compared with non-smokers. Another study reported a reduced risk of recurrence (HR 0.44, 95% CI 0.31-0.62), disease-specific mortality (HR 0.42, 95% CI 0.29-0.63) and overall mortality (HR 0.69, 95% CI 0.52-0.91) for patients who quit smoking ≥10 years prior to diagnosis compared with current smokers. Patients who quit smoking <10 years before diagnosis did not experience improved outcomes relative to current smokers. Wang *et al.* (2014) reported that both cumulative smoking exposure and smoking cessation time were significantly associated with disease recurrence and disease-specific mortality. Kim *et al.* (2014) reported that there were no significant differences in recurrence or disease-specific mortality between never, former, and current smokers.

Treatment-related morbidity

One study of 623 patients treated with BCG therapy for recurrent high-grade NMIBC reported the effects of smoking status on BCG response. A response to BCG was defined as a negative cystoscopy and negative urine cytology six months after treatment. There were no differences in the probability of a complete response between never vs. past smokers vs. current smokers (77% vs. 76% vs. 77%, p=0.95). Adjustment for time since smoking cessation was not associated with BCG response.

One study reported recurrence rates in 328 patients who had received adjuvant intravesical BCG therapy. Former and never smokers had a similar risk of disease recurrence after BCG therapy, whereas current smokers had a reduced BCG response compared to never smokers (HR 1.62, 95% CI 1.00-2.60), although the p value was not statistically significant in the multivariate analysis (p=0.059). A subgroup analysis of 582 current smokers reported that BCG therapy was

independently associated with disease recurrence in current smokers (HR 1.44, 95% CI 1.01-2.04). Controlling for the effects of maintenance therapy did not change the result.

Health-related quality of life (including patient reported outcomes)

One study reported on the associations between pain and current smoking status among cancer patients due to begin chemotherapy treatment (Ditre *et al.*, 2011). Data was captured as part of a randomised trial of lifestyle interventions designed to improve quality of life during chemotherapy. Cross-sectional baseline data demonstrated that current smokers (M=3.04, SE=.23) report more severe pain than never smokers (M=2.28, SE=.16) (p<.01). There were no differences in pain severity between former smokers and either current or never smokers (see Table 8 for results). Current smokers (M=2.46, SE=.18) also reported experiencing greater interference from pain than never (M=1.79, SE=.12) or former smokers (M=1.84, SE=.10). There were no significant differences in pain-related distress between current smokers (M=1.31, SE=.21) and never smokers (M=.89, SE=.14) or former smokers (M=.91, SE=.12), although mean scores were higher in current smokers.

In this study only 6% of patients had a diagnosis of bladder cancer. A majority of the sample were diagnosed breast cancer (35%) and lung cancer (33%). The authors reported that analyses were repeated with lung cancer patients removed and effect sizes tended to be similar to those observed for the entire sample.

Evidence statements

Moderate quality evidence from one systematic review of 19 studies (Crivelli *et al.*, 2014) and three further observational studies (Kim *et al.*, 2014; Wyszynski *et al.*, 2014; Wang *et al.*, 2014) was identified (14,863 patients in total).

For patients treated with TURBT, nine out of 13 studies found a statistically significant association of smoking with disease recurrence. Two out of eight studies and two out of two studies, when stratified by smoking status and smoking exposure respectively, found statistically significant associations between smoking and disease progression. The only study that evaluated the influence of smoking on disease-specific survival revealed no association. Overall survival was reported by four studies, all of which showed no significant associations with smoking, except for one study which reported that continued smoking after diagnosis, but not former smoking, was associated with shorter overall survival compared to never smoking (Wyszynski *et al.*, 2014).

For patients treated with radical cystectomy, three out of seven studies found statistically significant associations of smoking status with recurrence. The same studies also found that smoking was associated with disease-specific survival and overall survival, with smoking history being an independent prognostic factor for overall survival in one study (HR 1.31, 95% CI 1.05-1.63). However, no distinction was made between former or current smokers. The systematic review reported that in one study a reduced risk of recurrence (HR 0.44, 95% CI 0.31-0.62), disease-specific mortality (HR 0.42, 95% CI 0.29-0.63) and overall mortality (HR 0.69, 95% CI 0.52-0.91) was found for patients who quit smoking ≥10 years prior to diagnosis compared with current smokers.

One study of 623 patients treated with BCG therapy for recurrent high-grade NMIBC reported the effects of smoking status on BCG response. A response to BCG was defined as a negative cystoscopy

and negative urine cytology six months after treatment. There were no differences in the probability of a complete response between never smokers vs. past smokers vs. current smokers (77% vs. 76% vs. 77%, p=0.95). Adjustment for time since smoking cessation was not associated with BCG response.

Low quality evidence was identified from one study which reported on the associations between pain and current smoking status among cancer patients due to begin chemotherapy treatment (Ditre *et al.*, 2011). Only 6% of the study population were diagnosed with bladder cancer. Current smokers reported more severe pain and greater interference from pain than never smokers. There were no differences in pain severity between former smokers and either current or never smokers. Current smokers also reported experiencing greater interference from pain than former smokers. Pain-related distress scores did not significantly differ between groups.

Table 6: Hazard Ratios (HRs) for outcome by category of smoking status for patients treated with TURBT

HR >1 favours reference group, HR <1 favours comparison group

*indicates references as reported in systematic review by Crivelli *et al.* (2014)

Study (n patients)	Mean/ Median follow-up (months)	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
Disease recurrence									
Allard 1995* N=368	23.7	Ta, 79; T1, 21; G1, 34; G2, 54; G3, 12	Re-TUR, NR; BCG, 17; chemo, 2	Never	Former	1.28	0.82-1.98		Univariate analysis
					Current	1.45	0.94-2.24		
Fleshner 1999* N=286	57	Ta, 52; T1, 31; Tis, 17; G1, 34; G2, 31; G3, 35	Re-TUR, 100; BCG, 23; chemo, NR	Ex-smoker	Continued	**1.40**	**1.03-1.91**	**p=0.03**	
					Quitter	0.99	0.78-1.26	p=0.89	
				Continued	Quitter	0.71	0.48-1.05	-	
Chen 2007* N=265	38	Ta, 62; T1, 38; LG, 73; HG, 27	Re-TUR, NR; BCG, 19; chemo, 58	Quitter	Non-smoker	**2.2**	**1.1–4.5**	**p=0.03**	All BCG and chemo patients received maintenance therapy, an additional 23% had irregular intravesical therapy schedules
					Ex-smoker	1.4	0.7–2.7	p=0.35	
					Continued smoker	**2.2**	**1.2–4.0**	**p=0.01**	
Gee 2009* N=67	NR	NR (all had Cis and/or high grade tumours)	Re-TUR, NR; BCG, 100; chemo, NR	Non-smoker	Current	3.20		p=0.05	Of BCG patients, 21% received maintenance
				Former	Current	**0.27**		**p=0.03**	
Gangwar 2010* N=135	14	G1, 50; G2/3, 50	Re-TUR, NR; BCG, 55; chemo, 0	Non-smokers	Smokers	**1.86**		**p=0.02**	Of BCG patients, 8% received maintenance
Hwang 2011* N=251	34	PUNLMP, 6; LG, 63; HG, 32	Re-TUR, NR; BCG, 50; chemo, 14	Non-smokers	Smokers	**1.63**		**p=0.02**	
Lammers 2011* N=718	30	Ta, 79; T1, 21; G1, 42; G2, 47; G3, 11	Re-TUR, NR; BCG, NR; chemo, 100	Non-smokers	Ex and current smokers (EORTC factors)	**1.47**	**1.00-2.15**	**p=0.048**	

Study (n patients)	Mean/ Median follow-up (months)	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
					Ex and current smokers (CUETO factors)	**1.57**	**1.06-2.31**	**p=0.022**	
Rink 2013a* N=2043	49	Ta,61; T1, 39; G1, 24; G2, 34; G3, 43	Re-TUR, NR; BCG, 16; chemo, 4	Non-smokers	Former smokers	1.12	0.94-1.34	p=0.12	Of BCG and chemo patients, 47% received maintenance
					Current smokers	**1.22**	**1.01-1.48**		
Rink 2013a* N=1549 'ever' smokers				Current	Former smokers <10years	**1.30**	**1.09-1.53**	**p<0.001**	
					Former smokers ≥10years	**0.66**	**0.52-0.84**		
Rink 2013a* N=328, received BCG	42	NR	-	Non-smokers	Former smokers	1.06	0.65-1.71	p=0.059	Analysis of 328 patients who received adjuvant intravesical BCG immunotherapy
					Current smokers	1.62	1.00-2.60		
Rink 2012b* N= 582 current smokers	-	-	-	No BCG therapy	BCG therapy	1.44	1.01-2.04	**p=0.044**	Subgroup analysis of Rink (2013a)
Rink 2012a* N= 299 'ever' smokers	66	Ta,68; T1, 31; Tis, 1.5; G1, 37; G2, 29; G3, 34	Re-TUR, NR; BCG, 15; chemo, 3	Current smokers	Former smokers ≤9.9years	1.44	0.99-2.08	p=0.053	All BCG patients received maintenance therapy. No difference in recurrence between never, former and current smokers in univariate analysis
					Former smokers ≥10years	**0.4**	**0.24-0.67**	**p<0.001**	
				Light short-term[1] smoking exposure	Moderate smoking exposure	**2.08**	**1.23-3.49**	**p=0.006**	
				Light short-term smoking exposure	Heavy long-term exposure	**4.31**	**2.43-7.62**	**p<0.001**	

[1] Cumulative smoking exposure was categorized as light short-term (19 or fewer cigarettes per day and 19.9 years or less); moderate (all combinations except light short-term and heavy long-term); heavy long-term (20 or greater cigarettes per day and 20 years or greater).

Study (n patients)	Mean/ Median follow-up (months)	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
Sfakianos 2011* N=623	80.9	Ta,35; T1, 35; Tis, 30; LG, 10; HG, 90	Re-TUR, 100; BCG, 100; chemo, NR	Smoker	Non-smoker	1.05	0.84-1.31	p=0.68	Univariate analyses. No patients received maintenance BCG.
				Never smoked	Ex-smoker	1.05	0.84-1.32	p=0.65	
					Current smoker	1.04	0.77-1.40	p=0.81	
				Never smoked	Stopped>10 years	1.06	0.83-1.35	p=0.64	
					Stopped 0.1-10 years	1.22	0.90-1.66	p=0.20	
					Stopped at diagnosis	0.75	0.49-1.16	p=0.20	
					Current smoker	1.04	0.77-1.40	p=0.82	
Ajili 2012* N=112	Follow-up performed for 30 months	Ta,61; T1, 39; G1, 39; G2, 44; G3, 17	Re-TUR, NR; BCG, 100; chemo, NR	Non-smoker	Smoker	0.49		p=0.06	All BCG patients received maintenance
Serretta 2013* N=395	48	Ta,37; T1, 63; G1, 36; G2,64	Re-TUR, NR; BCG, NR; chemo, 100	Never smokers	Smokers (current + former)	**1.60**	-	**p=0.04**	Of chemo patients, 47% received maintenance. End-point of recurrence-free survival
Wyszynski 2013 N=726	72	TaT1 low grade, 74; TaT1 high grade, 20; Tis, 6	Re-TUR, NR; BCG, NR; chemo, NR; TUR+other, 16	Never smokers	Former smokers	**1.61**	**1.17-2.20**	**p=0.003**	
					Current smokers	**1.51**	**1.08-2.13**	**p=0.018**	
Disease progression									
Cheng 1999* N=83	64.8	T1, 100; LG, 34; HG, 66	Re-TUR, NR; BCG, 13; chemo, 19; radiation 1	Current versus former versus never smokers		-	-	p=0.22	Univariate analysis
Fleshner 1999* N=286	57	Ta, 52; T1, 31; Tis, 17; G1, 34; G2, 31; G3, 35	Re-TUR, 100; BCG, 23; chemo, NR	Ex-smoker	Continued	1.46	0.98-2.14	p=0.06	End-point was survival free of adverse event, defined as disease progression o other urinary tract TCC.
					Quitter	1.18	0.74-1.18	p=0.47	
Chen 2007*	36	Ta, 62; T1, 38; LG,	Re-TUR, NR;	Current	Former	-	-	p=0.43	Univariate analysis. All BCG and chemo

Study (n patients)	Mean/ Median follow-up (months)	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
N=265		73; HG, 27	BCG, 19; chemo, 58		Never	-	-	p=0.29	patients received maintenance therapy
					Quitter	-	-	**p=0.02**	
Gangwar 2010* N=135	14	G1, 50; G2/3, 50	Re-TUR, NR; BCG, 55; chemo, 0	Non-smokers	Smokers	1.96		p=0.39	Of BCG patients, 8% received maintenance
Hwang 2011* N=251	34	PUNLMP, 6; LG, 63; HG, 32	Re-TUR, NR; BCG, 50; chemo, 14	Non-smokers	Smokers	-	-	p=0.21	Univariate analysis
Rink 2013a* N=2043	49	Ta,61; T1, 39; G1, 24; G2, 34; G3, 43	Re-TUR, NR; BCG, 16; chemo, 4	Non-smokers	Former smokers	1.29	0.79-2.09	**p=0.003**	Of BCG and chemo patients, 47% received maintenance
					Current smokers	**2.09**	**1.29-3.39**		
Rink 2013a* N=1549 'ever' smokers				Current	Former smokers <10years	0.99	0.65-1.50	**p=0.036**	
					Former smokers ≥10years	**0.42**	**0.22-0.83**		
Rink 2012a* N= 299 'ever' smokers	66	Ta,68; T1, 31; Tis, 1.5; G1, 37; G2, 29; G3, 34	Re-TUR, NR; BCG, 15; chemo, 3	Current smokers	Former smokers ≤ 9.9 years	1.26	0.67-2.39	p=0.48	No difference in progression between never, former and current smokers in univariate analysis
					Former smokers ≥10 years	0.51	0.22-1.16	p=0.11	
				Light short-term[2] smoking exposure	Moderate smoking exposure			**p=0.003**	Only trend reported as no patient progressed in the group of light short-term smokers
					Heavy long-term exposure				
Sfakianos 2011* N=623	80.9	Ta,35; T1, 35; Tis, 30; LG, 10; HG, 90	Re-TUR, 100; BCG, 100;	Smoker	Non-smoker	1.02	0.66-1.59	p=0.93	Univariate analyses. No patients received maintenance BCG.
				Never smoked	Ex-smoker	1.00	0.64-1.58	p=0.99	

[2] Cumulative smoking exposure was categorized as light short-term (19 or fewer cigarettes per day and 19.9 years or less); moderate (all combinations except light short-term and heavy long-term); heavy long-term (20 or greater cigarettes per day and 20 years or greater).

Study (n patients)	Mean/ Median follow-up (months)	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
			chemo, NR		Current smoker	1.16	0.65-2.10	p=0.61	
				Never smoked	Stopped>10 years	1.06	0.65-1.72	p=0.81	
					Stopped 0.1-10 years	0.95	0.51-1.77	p=0.86	
					Stopped at diagnosis	0.81	0.35-1.88	p=0.62	
					Current smoker	1.16	0.65-2.08	p=0.62	
Segal 2012* N=278	36	T1, 100; HG, 100	Re-TUR, 100; BCG, 36; chemo, NR	Non-smokers	Smokers	1.15		0.51	Univariate analysis. End point was disease worsening
Overall Survival									
Rink 2013a* N=2043	49	Ta,61; T1, 39; G1, 24; G2, 34; G3, 43	Re-TUR, NR; BCG, 16; chemo, 4	Non-smokers	Former smokers	1.10	0.86-1.41	p=0.69	Of BCG and chemo patients, 47% received maintenance
					Current smokers	1.12	0.85-1.47		
Rink 2013a* N=1549 'ever' smokers				Current	Former smokers <10years	1.02	0.79-1.30	p=0.98	
					Former smokers ≥10years	0.98	0.72-1.34		
Rink 2012a* N= 390	66	Ta,68; T1, 31; Tis, 1.5; G1, 37; G2, 29; G3, 34	Re-TUR, NR; BCG, 15; chemo, 3	Current	Former	-	-	p>0.05	Univariate analysis
				Former	Never	-	-	p>0.05	
Sfakianos 2011* N=623	80.9	Ta,35; T1, 35; Tis, 30; LG, 10; HG, 90	Re-TUR, 100; BCG, 100; chemo, NR	Smoker	Non-smoker	1.14	0.79-1.64	p=0.49	Univariate analyses. No patients received maintenance BCG.
				Never smoked	Ex-smoker	1.20	0.82-1.74	p=0.34	
					Current smoker	1.03	0.63-1.68	p=0.91	
				Never smoked	Stopped>10 years	1.34	0.90-1.98	p=0.15	
					Stopped 0.1-10 years	1.16	0.71-1.90	p=0.54	

Study (n patients)	Mean/ Median follow-up (months)	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
					Stopped at diagnosis	0.64	0.31-1.34	p=0.24	
					Current smoker	1.03	0.63-1.68	p=0.92	
Wyszynski 2013 N=726	72	TaT1 low grade, 74; TaT1 high grade, 20; Tis, 6	Re-TUR, NR; BCG, NR; chemo, NR; TUR+other, 16	Never smokers	Former smokers	1.69	0.70-4.10	-	
					Current smoker	**3.42**	**1.29-9.07**	-	
Disease-specific survival									
Sfakianos 2011* N=623	80.9	Ta,35; T1, 35; Tis, 30; LG, 10; HG, 90	Re-TUR, 100; BCG, 100; chemo, NR	Smoker	Non-smoker	1.15	0.68-1.96	p=0.61	Univariate analyses. No patients received maintenance BCG.
				Never smoked	Ex-smoker	1.14	0.66-1.97	p=0.63	
					Current smoker	1.27	0.64-2.53	p=0.49	
				Never smoked	Stopped>10 years	1.29	0.72-2.29	p=0.39	
					Stopped 0.1-10 years	0.96	0.45-2.06	p=0.92	
					Stopped at diagnosis	0.80	0.30-2.18	p=0.67	
					Current smoker	1.27	0.64-2.52	p=0.49	
Treatment-related morbidity BCG response									
Sfakianos 2011* N=623	80.9	Ta,35; T1, 35; Tis, 30; LG, 10; HG, 90	Re-TUR, 100; BCG, 100; chemo, NR	Smoker	Non-smoker	0.75	0.48-1.19	p=0.22	Univariate analyses. No patients received maintenance BCG.
				Smoking status categorised 1, p=0.55					
				Never smoked	Ex-smoker	0.78	0.49-1.24	p=0.29	
					Current smoker	0.90	0.48-1.68	p=0.73	
				Smoking status categorised 2, p=0.07					
				Never smoked	Stopped>10 years	0.86	0.52-1.42	p=0.55	
					Stopped 0.1-10 years	**0.49**	**0.27-0.89**	**p=0.02**	
					Stopped at	1.55	0.60-4.05	p=0.37	

Study (n patients)	Mean/ Median follow-up (months)	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
					diagnosis				
					Current smoker	0.90	0.48-1.68	p=0.73	

Table 7: Hazard Ratios (HRs) for outcome by category of smoking status for patients treated with radical cystectomy

HR >1 favours reference group, HR <1 favours comparison group

*indicates references as reported in systematic review by Crivelli *et al.* (2014)

Study (n patients)	Follow-up mean/ median months	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
Recurrence									
Boorjian 2011* N=1506	162	T0-T1, 30; T2, 38; T3/T4, 32	Neoadj/adj, 11	Non-smokers	Smokers	0.97		p=0.87	End-point was urethral recurrence
Yafi 2011* N=2287	29.3	T0-T2, 51; T3/T4, 49; LG, 10; HG, 90	Neoadj, 3; Adj, 18	Non-smoker	Smoker			**p=0.006**	Univariate analysis
Lee 2012* N=602	56	T0-T2, 57; T3/T4, 43; G1/G2, 16; G3, 84	Neoadj, 0; Adj, NR	Smoker	Non-smoker	0.94	-	p=0.697	Smoking exposure known for 86% of patients
				Non-smoker	Ex-smoker	0.93	0.66-1.29	p=0.65	
					Current smoker	0.91	0.63-1.31	p=0.61	
				Non-smoker	>10.1 years since cessation	1.04	0.45-2.38	p=0.94	
					5.1-10 years since cessation	0.97	0.44-2.12	p=0.94	
					1.1-5 years since cessation	1.06	0.53-2.12	p=0.86	
					0.1-1 years since cessation	0.96	0.64-1.44	p=0.84	
					Current smoker	0.85	0.59-1.21	p=0.36	
Baumann 2013* N=442	26.4	T0 8; Ta, 2; Tis, 15; T1, 8; T2, 19; T3, 32; T4, 16	Neoadj, 9; Adj, 24	Non-smokers	Smokers	0.89		p=0.65	Univariate analysis
Rink 2013b* N=1506	34.3	T0 5; Ta, 4; Tis, 11; T1, 11; T2, 27;	Neoadj, 0; Adj, 21	Never smokers	Former smokers	1.26	0.96-1.66		
					Current smokers	**1.47**	**1.12-1.94**		

Study (n patients)	Follow-up mean/ median months	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
		T3, 31; T4, 11; LG, 2; HG, 93		Current	Former <10years	1.08	0.88-1.33	**<0.001**	
					Former ≥10years	**0.44**	**0.31-0.62**		
				Light short-term	Heavy short-term	**1.54**	**1.08-2.19**	**<0.001**	
					Light long-term	**1.70**	**1.23-2.36**		
					Heavy long-term	**2.22**	**1.62-3.02**		
Kim 2014 N=139	40	T0, 17; Tis, 16; T1, 8; T2, 12; T3, 41; T4, 6	Neoadj, 100; Adj, NR	Never smoker	Former	1.24	0.66-2.31	p=0.6	Active smokers are any reported smoking within 1y of initial diagnosis
					Active	0.91	0.44-1.84		
Wang 2014 N=588	40	Ta-T1, 16; T2, 28; T3, 40; T4, 16; LG, 13; HG, 87	Neoadj, 0; Adj, NR	Never smoker	Former and current	**1.48**	-	**<0.001**	
				Former ≥10years	Current	**3.4**	**2.2–5.5**	**<0.001**	
					Former <10years	**2.8**	**1.7–4.4**		
				Light short-term	Light long-term	1.5	0.96–2.5	p=0.01	
					Heavy short-term	1.6	0.96–2.5		
					Heavy long-term	**2.3**	**1.4–3.7**		
Disease-specific survival									
Thrasher 1994* N=531	126	Ta, 6; Tis, 4; T1, 31; T2, 40; T3, 7; T4, 12; G1/2, 12; G3, 42; G4, 45	Neoadj, NR; Adj, NR	Non-smokers	Smokers			p=0.85	Univariate analysis
Yafi 2011* N=2287	29.3	T0-T2, 51; T3/T4, 49; LG, 10; HG, 90	Neoadj, 3; Adj, 18	Non-smokers	Smokers	**1.30**		**P=0.046**	
Lee 2012* N=602	56	T0-T2, 57; T3/T4, 43; G1/G2, 16; G3, 84	Neoadj, 0; Adj, NR	Smoker	Non-smoker	1.10	-	p=0.59	Smoking exposure known for 86% of patients
				Non-smoker	Ex-smoker	1.21	0.86-1.70	p=0.26	
					Current smoker	0.94	0.64-1.37	p=0.73	
				Non-smoker	>10.1 years since cessation	1.13	0.46-2.82	p=0.79	

Study (n patients)	Follow-up mean/ median months	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
					5.1-10 years since cessation	0.93	0.37-2.31	p=0.87	
					1.1-5 years since cessation	1.42	0.77-2.62	p=0.26	
					0.1-1 years since cessation	1.17	0.78-1.75	p=0.45	
					Current smoker	1.17	0.64-2.13	p=0.61	
Bostrom 2012* N=546	50	T0-T1, 30; T2, 38; T3/T4, 32	Neoadj, NR; Adj, NR	Non-smokers	Smokers	1.1		p=0.41	
Rink 2013b* N=1506	26.4	T0 5; Ta, 4; Tis, 11; T1, 11; T2, 27; T3, 31; T4, 11; LG, 2; HG, 93	Neoadj, 0; Adj, 21	Never smokers	Former smokers	1.22	0.91-1.63		
					Current smokers	**1.41**	**1.04-1.90**		
				Current	Former <10years	1.09	0.86-1.37	**<0.001**	
					Former ≥10years	**0.42**	**0.29-0.63**		
				Light short-term	Heavy short-term	**1.55**	**1.04-2.32**	**<0.001**	
					Light long-term	**1.53**	**1.04-2.24**		
					Heavy long-term	**2.07**	**1.44-2.99**		
Kim 2014 N=139	40	T0, 17; Tis, 16; T1, 8; T2, 12; T3, 41; T4, 6	Neoadj, 100; Adj, NR	Never smoker	Former	0.90	0.40-2.03	P=0.9	Active smokers are any reported smoking within 1y of initial diagnosis
					Active	1.07	0.44-2.60		
Wang 2014 N=588	40	Ta-T1, 16; T2, 28; T3, 40; T4, 16; LG, 13; HG, 87	Neoadj, 0; Adj, NR	Never smoker	Former and current	**2.62**	-	**<0.001**	
				Former ≥10years	Current	**3.2**	**1.9–5.2**	**<0.001**	
					Former <10years	**2.3**	**1.4–3.9**		
				Light short-term	Light long-term	1.3	0.79–2.2	p=0.01	
					Heavy short-term	1.4	0.81–2.4		
					Heavy long-term	**2.2**	**1.3–3.6**		
Overall survival									

Study (n patients)	Follow-up mean/ median months	Patient stage/grade, %	Additional intervention, %	Reference group	Smoking status	Multivariate analysis			
						HR	95% CI	p-value	Comments
Yafi 2011* N=2287	29.3	T0-T2, 51; T3/T4, 49; LG, 10; HG, 90	Neoadj, 3; Adj, 18	Non-smoker	Smoker (current or ever)	**1.31**	**1.05-1.63**	**p=0.017**	
Bostrom 2011* N=546	50	T0-T1, 30; T2, 38; T3/T4, 32	Neoadj, NR; Adj, NR	Non smoker (no history of smoking)	Smoker (current and previous smokers)	1.3	0.9-1.7	p=0.095	
Lee 2012* N=602	56	T0-T2, 57; T3/T4, 43; G1/G2, 16; G3, 84	Neoadj, 0; Adj, NR	Smoker	Non-smoker	1.01	NR	p=0.93	
Rink 2013b* N=1506	26.4	T0 5; Ta, 4; Tis, 11; T1, 11; T2, 27; T3, 31; T4, 11; LG, 2; HG, 93	Neoadj, 0; Adj, 21	Never smokers	Former smokers	1.13	0.89-1.44		
					Current smokers	1.25	0.97-1.60		
				Current	Former <10years	1.05	0.85-1.28	**p=0.012**	
					Former ≥10years	**0.69**	**0.52-0.91**		
				Light short-term	Heavy short-term	1.23	0.90-1.69	**p=0.004**	
					Light long-term	**1.36**	**1.01-1.83**		
					Heavy long-term	**1.51**	**1.13-2.01**		

Table 8. Outcome data reported by Ditre et al. (2011)

N=224 (Never smokers (n=80) >100 cigarettes in lifetime; Former smokers (n=108) quit smoking and not smoked in past month; Current smokers (n = 36) who had smoked in past month)		
Outcomes	**Comparison**	**P values**
Pain severity – SF-36 Bodily Pain subscale (range of scores 1=none, to 6=very severe)	Current smokers (M=3.04, SE=.23) vs never smokers (M=2.28, SE=.16) Former smokers (M=2.59, SE=.13) vs current or never smokers	**p<0.01** p≥0.09
Pain interference – SF-36 Bodily Pain subscale (range of scores 1=not at all, to 5=extremely)	Current smokers (M=2.46, SE=.18) vs never smokers (M=1.79, SE=.12) Current smokers vs former smokers (M=1.84, SE=.10) Former smokers vs never smokers	**p<0.01** **p<0.01** p=0.79
Pain-related distress – Memorial Symptom Assessment Scale (range of scores 0=not at all, to 4=very much)	Current smokers (M=1.31, SE=.21) vs never smokers (M=.89, SE=.14) Current smokers vs former smokers (M=.91, SE=.12)	Non-significant (p values not stated) Non-significant (p values not stated)

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Reason for exclusion: not relevant to PICO

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Reason for exclusion: duplicate of included study

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Reason for exclusion: expert review

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Reason for exclusion: superseded by Crivelli (2014) systematic review

Aveyard, P et al. Does smoking status influence the prognosis of bladder cancer? A systematic review. BJU International 2002; 90(3): 228-239.

Evidence tables

Study Study type	Population	Method	Prognostic factor	Median follow-up	Outcomes	Results	Additional comments
Crivelli 2014 Systematic review	Patients with urothelial carcinoma of the bladder treated with either transurethral resection of the bladder (TURBT) or radical cystectomy (RC)	Systematic review of studies published 1974-March 2013. Included: patients with significant smoking history of smoking exposure compared with lesser smoking history of smoking exposure. Excluded case reports, non-English language papers, review articles, meeting abstract, editorials and commentary. Studies combining patients who received TURBT and RC and studies with ≤10 participants in exposure or comparator group were excluded.	The following categories of smoking status were reported: non-smokers or never smokers; former smokers; current smokers. In studies including a quitter category, former smokers stopped smoking ≥1y prior to diagnosis and quitters stopped smoking between 1y before and 3mo after diagnosis.	Varied across studies	For those treated with TURBT recurrence defined as relapse in the bladder; Progression defined as a muscle-invasive relapse in the bladder. For those treated with RC, recurrence was defined as a local or distant tumour relapse. Cancer-specific mortality; Any-cause mortality. Response to intravesical therapy, Impact of smoking cessation	14 studies assessed impact of smoking on outcomes of patients treated with TURBT plus an additional study that evaluated response to BCG.	Review also included studies of patients with upper tract cancer but this data was not relevant to the review question. No quality assessment of included studies. Meta-analysis not performed due to heterogeneity across cohorts. Studies of TURBT varied in patient population and follow-up time. Use of intravesical therapy and repeat TURB also varied and was often not reported. Use of neoadjuvant/adjuvant chemotherapy varied across studies of patients treated with RC.
Wyszynski 2014 Observational study	726 patients with NMIBC 76% male, 24% female 74% TaT1 low grade, 20% TaT1 high grade, 6% Tis 75% TURBT, 16% TURBT+other, 9% other	Aimed to analyse the relationship between cigarette smoking and bladder cancer recurrence for patients with smoking data at diagnosis. Follow-up	Smoking status available on 716 NMIBC coded as never smoker, former smoker (quit at or before diagnosis), continuing	6 years (range 3mo to 15y)	Recurrence; Progression; Overall survival	Smoking associated with a shorter time to first recurrence. No difference in progression, although	'Other' treatment not specified.

Study Study type	Population	Method	Prognostic factor	Median follow-up	Outcomes	Results	Additional comments
		questionnaire given to surviving respondents (n=448) to collect updated smoking information.	smoker (smokers who continued to smoke after diagnosis)			statistical power was limited (no data provided) Continued smoking after diagnosis but not former smoking, was associated with shorter overall survival.	
Kim 2014 Retrospective review	139 patients with MIBC (T2-T4a N0M0) who received cisplatin-based neoadjuvant chemotherapy and radical cystectomy. Median age 65 y. 71% male, 29% female.	Smoking history collected from record of initial consultation. Recurrence and survival determined from chart review	Smoking status: 29% active (smoking at diagnosis or quit within 1 year of diagnosis) 45% former, 25% never smoker)	For those who did not recur = 46 months, for those who did not die=40 months	Recurrence-free survival; Cancer-specific survival	No association between smoking and recurrence of cancer-specific death.	Primary outcome was response to Cisplatin-based chemotherapy
Ditre 2011 Cross-sectional data obtained as part of RCT USA	224 patients scheduled to receive CT. Male 37%/ Female 63%. 10% Stage I 26% stage II 30% Stage III 34% Stage IV All patients due to receive chemotherapy	Cross-sectional questionnaire. Patient reported smoking status and pain severity which was correlated with self-reported pain outcomes.	Never smokers (n=80) >100 cigarettes in lifetime; Former smokers (n=108), quit smoking and not smoked in past month; Current smokers (n = 36) smoked in past month	n/a	Pain severity and pain inference (SF-36) Pain related distress (Memorial Symptom Assessment Scale-Short Form (MSAS-SF)	Current smokers (M=3.04, SE=.23) report more severe pain than never smokers (M=2.28, SE=.16) (p<.01). There were no differences in pain severity between former smokers and either current or never smokers. Current smokers (M=2.46, SE=.18) also reported experiencing greater interference from pain than never (M=1.79, SE=.12) or former smokers (M=1.84,	Majority of sample breast cancer (35%) and lung cancer (33%), which limits applicability to review question population

Study Study type	Population	Method	Prognostic factor	Median follow-up	Outcomes	Results	Additional comments
						SE=.10). There were no significant differences in pain-related distress between current smokers (M=1.31, SE=.21) and never smokers (M=.89, SE=.14) or former smokers (M=.91, SE=.12).	
Wang 2014 USA Observational study	668 patients who underwent RC and bilateral lymphadenectomy for UCB from 1995-2005 at 5 participating institutions. The study targeted 588 patients who did not receive neoadjuvant chemotherapy or radiotherapy (n =80). Median age 65 y (IQR, 59-72) 84% male, 16% female 16% pTa-T1, 28% pT2, 40% pT3, 16% pT4 13% LG, 87% HG	Self-reported smoking data were routinely assessed at the clinical visit before RC Cause of death was determined by treating physicians by chart review corroborated by death certificates or by death certificates alone	Smoking characteristics analyzed include smoking status(never, former, or current smoker), duration of smoking (≤10, 11–20, 21–30, or >30 y), quantity of smoking(1–10, 11–20, 21–30, or >30 cigarettes per day[CPD]), years since cessation (current, <10, ≥10), cumulative smoking exposure(light short term ≤20 CPD for ≤20 y, heavy short-term >20 CPD for ≤20 y, light long term ≤20 CPD for >20 y, and heavy long-term >20 CPD for>20 y)	In former smokers, a median follow-up of 40 months. In current smokers, a median follow-up of 48 months	**Disease recurrence** was defined as tumour relapse in the operative field, regional lymph nodes, or distant organs. **Cancer-specific mortality**	In multivariable analyses, smoking status (never, former, and current smokers) was independently associated with disease recurrence and cancer-specific death (HR =1.48 and 2.62, for former and current smokers vs. Never smokers, respectively; both P <0.001). Smoking duration (P=0.06and P =0.3) and cigarette quantity (P = 0.08 and P = 0.1) were not significantly associated with disease recurrence and cancer-specific mortality. Both cumulative smoking exposure (both P =	Study also assessed prognostic value of molecular markers – this data was not relevant to the review question and was not extracted

Study Study type	Population	Method	Prognostic factor	Median follow-up	Outcomes	Results	Additional comments
						0.01) and smoking cessation time (both P <0.001) were significantly associated with disease recurrence and cancer-specific mortality.	

2 Diagnosing and staging bladder cancer

2.1 Endoscopic Assessment

Review question: What are the most effective endoscopic techniques for diagnosing bladder cancer (for example white light, blue light, narrow band cystoscopy)?

Rationale

The diagnosis of bladder cancer is usually made visually using a telescope inserted into the bladder (cystoscopy) with the patient awake as an outpatient. Until recently it was assumed that the standard procedure, white light cystoscopy (WLC) was accurate but it is now accepted that this will miss some bladder cancers. One particular type of bladder cancer called carcinoma in situ (CIS) although rare is easy to miss when using WLC.

There are two new techniques to aid the visual diagnosis of bladder cancer at cystoscopy – photodynamic diagnosis/blue light cystoscopy (PDD) and narrow band imaging (NBI).

The topic is contentious because both techniques are relatively new and only available in a small number of hospitals. There are no direct randomised trials to compare the two techniques against each other. Furthermore it is not known which groups of bladder cancer patients would benefit most from these techniques.

This review should establish the overall effectiveness of PDD and NBI for diagnosing bladder cancer when compared with WLC. The cost effectiveness of both techniques should be reviewed and guidance given as to which subgroups of bladder cancer patients would benefit most from these techniques.

Question in PICO format

Population	Index tests	Reference standard	Outcomes
Patients with suspected bladder cancer (new or recurrent)	White light cystoscopy Narrow band cystoscopy Blue light cystoscopy/ Photodynamic diagnosis (PDD) Alone or in combination	Histopathological examination of biopsied tissue	• Diagnostic yield • Sensitivity • Specificity • Process-related morbidity • Health-related quality of life

METHODS

Information sources

A relevant Health Technology Assessment (HTA) was published in 2010 (Mowatt *et al.*, 2010), which reviewed the diagnostic accuracy of photodynamic diagnosis (PDD) and white light cystoscopy (WLC). 27 studies (from 36 reports) were included in the HTA review. The HTA search for PDD and WLC was updated for this evidence review. A search was also conducted for narrow band imaging with no date limit.

Selection of studies

The same exclusion and inclusion criteria as specified in the HTA were used to screen identified studies. To be included, studies reporting test performance had to report the absolute numbers of true positives, false positives, false negatives and true negatives, or provide information allowing their calculation. The reference standard for studies of diagnostic accuracy was histopathological examination of biopsied tissue. Studies reported as abstracts only were excluded. Evidence about recurrence was gathered from one systematic review of raw data of WLC and Hexaminolevulinate (HAL) PDD (Burger *et al.*, 2013) and one randomised trial of NBI and WLC (Naselli *et al.*, 2012).

Data synthesis

Only four PDD/WLC studies reporting sufficient information to be included in the HTA update were identified from the search. In all four studies the sensitivity of PDD was higher than WLC, and specificity was higher for WLC compared to PDD in two out of four studies. Due to the small number of new studies, it was not considered necessary to update the HTA pooled analyses. For patient and biopsy-level analysis, pooled estimates with 95% confidence intervals (CI) for sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios (DORs) were presented. For stage/grade level of analysis the median (range) sensitivity across studies were presented. Studies reporting patient and biopsy-level analysis for carcinoma in situ (CIS) were included in the section on stage/grade analysis. In the HTA, test performance was presented in terms of the detection of stage and grade of non- muscle-invasive bladder cancer in two broad categories: (1) less aggressive, lower risk tumours (pTa, G1, G2) and (2) more aggressive, higher risk tumours (pT1, G3, CIS). For this evidence review, the median (range) sensitivity across studies for muscle invasive cancer (≥pT2) was also calculated.

In the HTA, meta-analyses were fitted using the HSROC model using the NLMIXED function. This HSROC model takes account of the diseased and non-diseased sample sizes in each study and allows estimation of random effects for the threshold and accuracy effects.

For the outcome of recurrence, data from the systematic review of PDD versus WLC is presented. Three further studies were also added to the meta-analysis using RevMan.

RESULTS

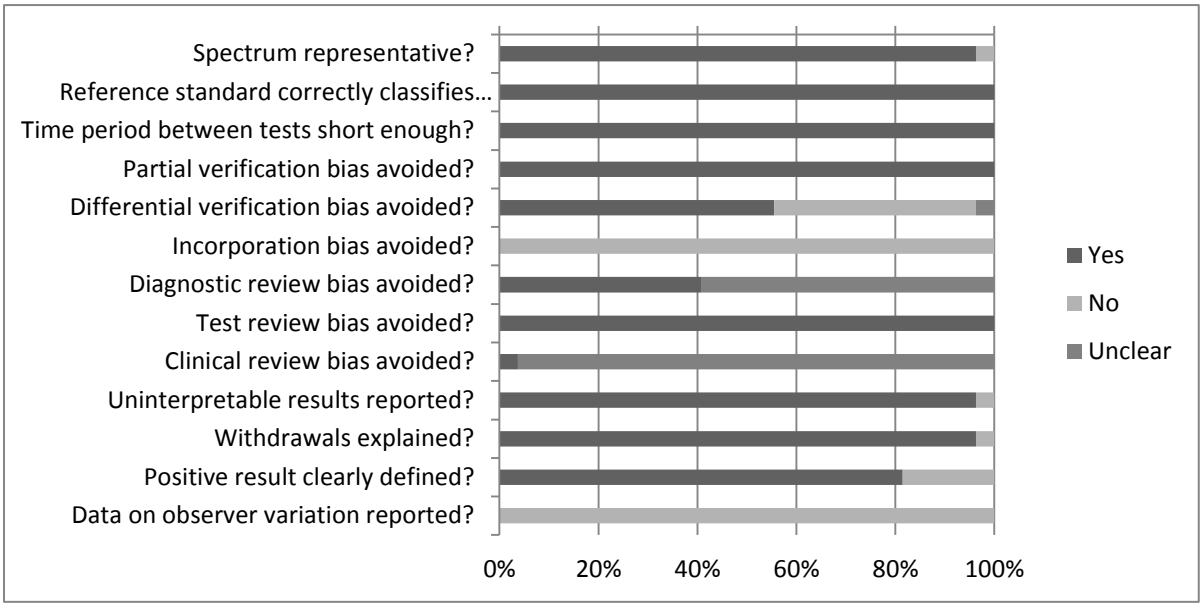
Result of the literature searches

Figure 5. Study flow diagram

Study quality and results

A Health Technology Assessment (HTA) was identified (Mowatt *et al.*, 2010), which reviewed the diagnostic accuracy of photodynamic diagnosis (PDD) and white light cystoscopy (WLC). 27 studies (from 36 reports) were included in the HTA review and a further four studies were identified from the literature search. The methodological quality of the included studies was assessed using a modified version of the QUADAS tool containing 13 questions. The results of the quality assessment are provided in Figure 6. In all studies partial verification bias was avoided (all patients received a reference standard test) and test review bias was avoided (PDD and WLC were interpreted without knowledge of the results of the reference standard test). In 96% (26/27) of studies uninterpretable or intermediate test results were reported or there were none, and withdrawals from the study were explained or there were none. However, all of the studies were judged to suffer from incorporation bias in that PDD was considered not to be independent of the reference standard test as biopsies used in the reference standard test were obtained via the PDD procedure.

Figure 6. Summary of quality assessment of PDD/WLC diagnostic studies



The quality of the included studies in Zheng *et al.* (2012) was assessed by the QUADAS tool. According to the QUADAS assessment, all of the included studies scored >9 points (out of 11), indicating that they were of good quality.

A summary of the pooled estimate results from the HTA are shown in Tables 9 and 10. A systematic review of the diagnostic accuracy of narrow band imaging (NBI) and WLC was identified (Zheng *et al.*, 2012) and the results are provided in Tables 11, 12, and 13. Evidence for recurrence was gathered from one systematic review of raw data of WLC and Hexaminolevulinate (HAL) PDD (Burger *et al.*, 2013) and one randomised trial of NBI and WLC (Naselli *et al.*, 2012). Recurrence data is provided in Tables 14-15, and Figures 7-8.

Evidence statements

PDD versus WLC

Diagnostic accuracy

In both patient and biopsy based detection of bladder cancer PDD had a higher sensitivity but lower specificity than WLC (Mowatt *et al.*, 2010). Five studies (370 patients) reported patient-based detection. In the pooled estimates the sensitivity for PDD was 92% (95% CI 80% to 100%) compared with 71% (95% CI 49% to 93%) for WLC, whereas the specificity for PDD was 57% (95% CI 36% to 79%) compared with 72% (95% CI 47% to 96%) for WLC, with the CIs for the two techniques overlapping. A total of 14 studies (1746 patients) reported biopsy-based detection (number of biopsies: 8574 for PDD analysis, 8473 for WLC analysis). In the pooled estimates the sensitivity for PDD was 93% (95% CI 90% to 96%) compared with 65% (95% CI 55% to 74%) for WLC, whereas the specificity for PDD was 60% (95% CI 49% to 71%) compared with 81% (95% CI 73% to 90%) for WLC. The pair of CIs for both sensitivity and specificity did not overlap, providing evidence of a difference in diagnostic performance between the techniques. The point estimates of the patient-level analysis were similar to those from the biopsy-level analysis, although the intervals were substantially wider,

as might be expected because of the smaller number of studies and observations available for this level of analysis.

For less aggressive, lower risk tumours (pTa, G1, G2), the median sensitivities for PDD and WLC were broadly similar for patient-based detection, and higher for PDD than WLC for biopsy-based detection. For more aggressive, higher risk tumours, the median sensitivity of PDD was higher than WLC for both patient and biopsy-based tumour detection. When CIS was considered separately, the median sensitivity of PDD for detecting CIS was much higher than that of WLC, for both patient and biopsy-based detection. However, these results should be interpreted with caution as some of the median sensitivities are based on a small number of studies/patients.

PDD versus WLC

Side effects of photosensitising agent used

The HTA by Mowatt *et al.* (2010) reported that 18 studies used 5-ALA as the photosensitising agent. Seven studies (1320 patients) reported that no side-effects were associated with the instillation of 5-ALA. Five studies used HAL as the photosensitising agent. Two studies reported adverse events in 40 out of 52 and 4 out of 20 patients, respectively, although none was considered to be related to the HAL instillation.

PDD versus WLC

Recurrence

Moderate quality evidence from the systematic review by Burger *et al.* (2013) reported that in all three studies included in the meta-analysis, HAL cystoscopy was associated with lower recurrence. The overall recurrence rate was 34.5% PDD versus 45.4% WLC (RR 0.76, 95% CI 0.63 to 0.92), in favour of HAL cystoscopy. One study (Geavlete *et al.*, 2011) was excluded from the meta-analysis by Burger *et al.* (2013) as no raw data was provided. Two further studies (Karaolides *et al.*, 2012; O'Brien *et al.*, 2013) were published after the meta-analysis by Burger *et al.* (2013) was conducted. The published data from these three studies were added to the meta-analysis which reduced the effect estimate and 95% CIs further in favour of PDD (RR 0.69, 95% CI 0.58 to 0.82).

NBI versus WLC

Diagnostic accuracy

Zheng *et al.* (2012) used the I^2 index to describe the percentage of variation across studies that was due to heterogeneity rather than chance. The authors reported significant heterogeneity among studies for NBI and WLC analysis, with I^2 values all above 75%, indicating high heterogeneity. Due to the low number of studies, a meta-regression and subgroup analyses could not be performed to identify the sources of heterogeneity.

Five studies (759 patients) were pooled for NBI in a patient level analysis. The pooled sensitivity and specificity of NBI were 94% (95% CI 91% to 96%) and 85% (95% CI 81% to 88%). Three studies (648 patients) were included in the pooled patient level estimates for WLC. The pooled sensitivity and specificity for WLC were 85% (95% CI 80% to 89%) and 87% (95% CI 83% to 90%).

Four studies (341 patients, 1195 biopsies) were included in the pooled biopsy level analysis for NBI and WLC. The pooled sensitivity and specificity for NBI were 95% (95% CI 93% to 96%) and 55% (95% CI 50% to 59%). The pooled sensitivity and specificity for WLC were 75% (95% CI 72% to 78%) and 72% (95% CI 68% to 76%).

Therefore, NBI had a higher sensitivity than WLC in both the patient level and biopsy level analyses, with no overlap between CIs. NBI had a lower specificity than WLC in both the patient level and biopsy level analyses. 95% CIs did not overlap in the biopsy level analysis, providing evidence of a difference in diagnostic performance between the two tests.

NBI versus WLC

Recurrence

Moderate quality evidence from one prospective randomised trial of 148 patients (Naselli *et al.*, 2012) comparing TUR performed with NBI or WL, reported a 12-month recurrence rate of 32.9% (25/76) in the NBI group and 51.4% (37/72) in the WL group (RR 0.64, 95% CI 0.43 to 0.95).

Process-related morbidity/Health-related quality of life

A cross-sectional questionnaire study was conducted as part of a randomised trial (van der Aa *et al.*, 2008), which assessed patient-reported perceived burden of cystoscopic and urinary surveillance (low quality evidence). Patients completed questionnaires one week after cystoscopy or one week after collection of a urine sample for microsatellite analysis. 732 questionnaires completed by 197 patients were available for cystoscopy. The introduction of the cystoscope was considered most often burdensome, being at least quite discomforting in 39% of the questionnaires, and at least quite painful in 35% of the questionnaires. Painful voiding of urine was reported in 31% of cases after cystoscopy, urge and frequency were reported in 35% of questionnaires. Haematuria and fever occurred infrequently. After cystoscopy, at least a little impact on daily activities was reported in 134/720 (19%) of the questionnaires, and at least a little impact on social activities were reported in 86/723 (12%). Overall burden was calculated from the items on pain and discomfort with scores ranging from one (no burden) to three (much burden). The mean overall burden was 1.33 (SE = 0.017). Increasing age was associated with less reported overall burden of cystoscopy.

Table 9. Summary of pooled estimate results for PDD and WLC for patient-based detection of bladder cancer (reported in Mowatt et al., 2010)

Test	No. of studies	No. analysed	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
PDD	5	370	92 (80 to 100)	57 (36 to 79)	16.50 (1.00 to 42.23)	2.17 (1.16 to 3.19)	0.13 (0.01 to 0.32)
WLC	5	370	71 (49 to 93)	72 (47 to 96)	6.44 (1.00 to 14.24)	2.57 (0.53 to 4.61)	0.40 (0.12 to 0.67)

Table 10. Summary of pooled estimate results for PDD and WLC for biopsy-based detection of bladder cancer (reported in Mowatt et al., 2010)

Test	No. of studies	No. analysed	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
PDD	14	1746	93 (90 to 96)	60 (49 to 71)	20.29 (9.20 to 31.37)	2.33 (1.73 to 2.92)	0.12 (0.06 to 0.17)
WLC	14	1746	65 (55 to 74)	81 (73 to 90)	7.76 (3.39 to 11.93)	3.38 (2.01 to 4.75)	0.44 (0.33 to 0.54)

Table 11. Summary of pooled estimate results for NBI and WLC for patient-based detection of bladder cancer (reported in Zheng, 2012)

Test	No. of studies	No. analysed	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)	Positive likelihood ratio	Negative likelihood ratio	AUC (standard error)
NBI	5	759	94 (91 to 96)	85 (81 to 88)	185.32 (45.71 to 751.26)	7.04 (3.36 to 14.75)	0.05 (0.01 to 0.24)	0.978 (0.015)
WLC	3	648	85 (80 to 89)	87 (83 to 90)	42.93 (8.09 to 227.88)	6.94 (2.05 to 23.47)	0.18 (0.09 to 0.36)	0.894 (0.08)

Table 12. Summary of pooled estimate results for NBI and WLC for biopsy-based detection of bladder cancer (reported in Zheng, 2012)

Test	No. of studies	No. analysed	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)	Positive likelihood ratio	Negative likelihood ratio	AUC (standard error)
NBI	4	341 (1195 lesions)	95 (93 to 97)	55 (50 to 59)	23.05 (9.23 to 57.55)	2.08 (1.26 to 3.45)	0.11 (0.07 to 0.17)	0.903 (0.067)
WLC	4	341 (1195 lesions)	75 (72 to 78)	72 (68 to 76)	5.88 (2.41 to 14.35)	2.49 (1.17 to 5.27)	0.42 (0.28 to 0.62)	0.768 (0.056)

Table 13. Summary of pooled estimate results for NBI for patient-based detection of CIS (reported in Zheng, 2012)

Test	No. of studies	No. analysed	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)	Positive likelihood ratio	Negative likelihood ratio	AUC (standard error)
NBI	4	719	93 (88 to 96)	77 (73 to 80)	48.88 (15.64 to 152.77)	4.55 (2.82 to 7.33)	0.13 (0.05 to 0.30)	0.94 (0.033)

Table 14. GRADE evidence profile: HAL PDD versus WLC

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDD	WLC	Relative (95% CI)	Absolute	
Recurrence (follow-up 9-12 months)											
3[1]	randomised trials	none	none	none	serious[2]	none	107/310 (34.5%)	147/324 (45.4%)	RR 0.76 (0.63 to 0.92)	109 fewer per 1000 (from 36 fewer to 168 fewer)	⊕⊕⊕O MODERATE
Recurrence (including other published data) (follow-up 9-12 months)											
6[3]	randomised trials	none	serious[4]	none	none	none	148/539 (27.5%)	219/550 (39.8%)	RR 0.69 (0.58 to 0.82)	131 fewer per 1000 (from 76 fewer to 177 fewer)	⊕⊕⊕O MODERATE
Recurrence (at least one T1 or CIS)											
1[5]	randomised trials	none	none	none	serious[6]	none	26/74 (35.1%)	45/87 (51.7%)	RR 0.68 (0.47 to 0.98)	166 fewer per 1000 (from 10 fewer to 274 fewer)	⊕⊕⊕O MODERATE
Recurrence (at least one Ta)											
1[5]	randomised trials	none	none	none	serious[6,7]	none	92/256 (35.9%)	119/268 (44.4%)	RR 0.81 (0.66 to 1.00)	84 fewer per 1000 (from 151 fewer to 0 more)	⊕⊕⊕O MODERATE
Recurrence (high risk subgroup)											
1[5]	randomised trials	none	none	none	serious[6,7]	none	46/126 (36.5%)	70/144 (48.6%)	RR 0.75 (0.56 to 1.00)	122 fewer per 1000 (from 214 fewer to 0 more)	⊕⊕⊕O MODERATE
Recurrence (intermediate risk subgroup)											
1[5]	randomised trials	none	none	none	serious[6,7]	none	43/95 (45.3%)	40/74 (54.1%)	RR 0.84 (0.62 to 1.14)	86 fewer per 1000 (from 205 fewer to 76 more)	⊕⊕⊕O MODERATE
Recurrence (low risk subgroup)											
1[5]	randomised trials	none	none	none	serious[6,7]	none	14/78 (17.9%)	34/98 (34.7%)	RR 0.52 (0.30 to 0.89)	167 fewer per 1000 (from 38 fewer to 243 fewer)	⊕⊕⊕O MODERATE

[1] From meta-analysis in Burger (2013)
[2] Low number of events limits precision
[3] From meta-analysis in Burger (2013) plus published data from Geavlete 2011; Karaolides 2012; O'Brien 2013
[4] Published data only from 3 studies.
[5] From meta-analysis in Burger (2013). Number of studies in subgroup analysis not reported.
[6] Low number of events
[7] Confidence interval includes null value

Table 15. GRADE evidence profile: NBI versus WLC

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NBI**	**WLC**	**Relative (95% CI)**	**Absolute**	
Recurrence (follow-up 12 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	25/76 (32.9%)	37/72 (51.4%)	RR 0.64 (0.43 to 0.95)	185 fewer per 1000 (from 26 fewer to 293 fewer)	⊕⊕⊕O MODERATE

[1] Naselli 2012

[2] Small sample size / Low number of events

Figure 7. PDD versus WLC. Outcome, Recurrence rate up to 12 months (Burger, 2013)

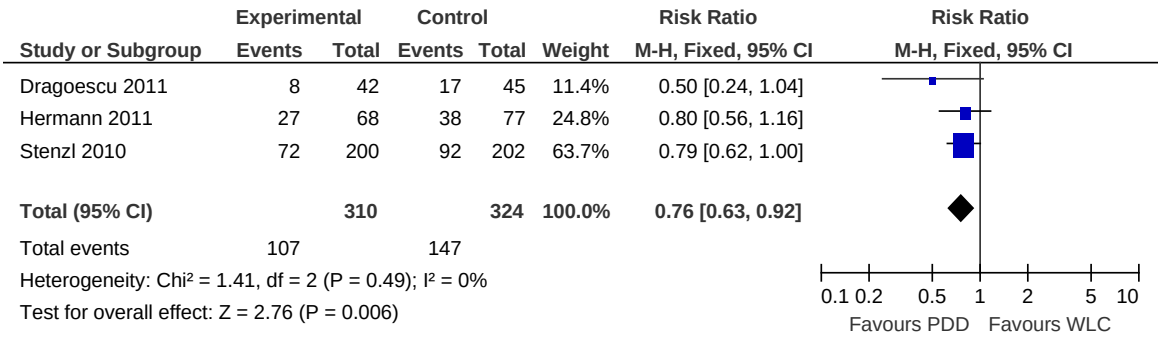
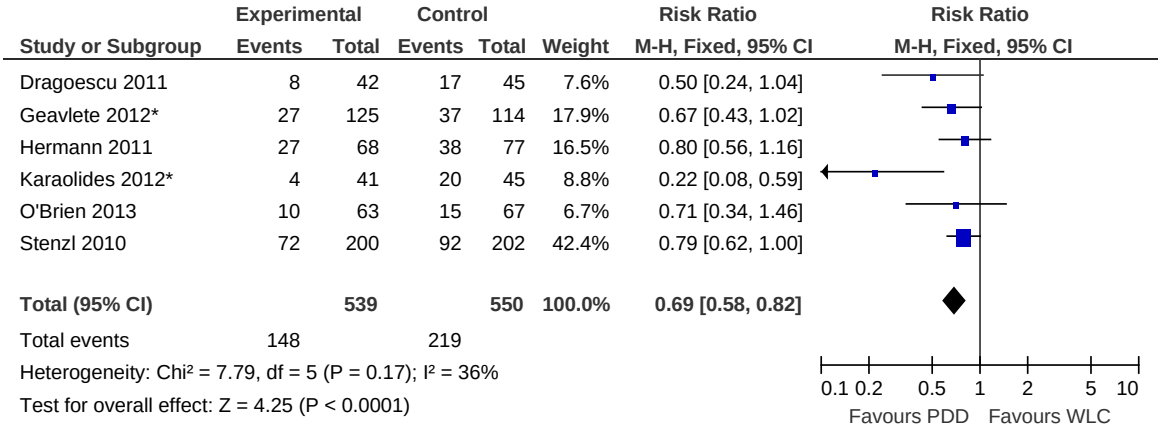


Figure 8. PDD versus WLC. Outcome, Recurrence rate up to 12 months (Including published data from Geavlete 2011; Karaolides 2012; O'Brien 2013).



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Volpe, A. Fluorescent cystoscopy with hexaminolevulinate: Assessment of the diagnostic accuracy for non-muscle-invasive bladder cancer. Anticancer Research 2010; 30(4): 1474-1474.

O'Brien, TS. A prospective randomised trial of Hexylaminolevulinate (Hexvix) assisted transurethral resection (TURBT) plus single shot intravesical mitomycin (MMC) versus conventional white light TURBT plus single shot MMC in newly presenting bladder cancer. European Urology, Supplements 2011; 10(2): 150-150.

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Mostafid, H, Bunce, C, and Action on Bladder Cancer Group. Improved detection and reduced early recurrence of non-muscle-invasive bladder cancer using hexaminolaevulinate fluorescence cystoscopy: results of a multicentre prospective randomized study (PC B305). BJU International 2009; 104(7): 889-890.

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Tatsugami, K. Detection of bladder cancer with narrow-band imaging system. Journal of Urology 2009; 181(4): 414-414.

Wu, QH et al. A prospective comparison of narrow-band imaging cystoscopy to standard white light cystoscopy in bladder cancer. BJU International 2014; 113: 17-18.

Reason: Animal study

Ren, H et al. Early detection of carcinoma in situ of the bladder: a comparative study of white light cystoscopy, narrow band imaging, 5-ALA fluorescence cystoscopy and 3-dimensional optical coherence tomography. Journal of Urology 2012; 187(3): 1063-1070.

Reason: Commentary

Montie, JE. Hexylaminolaevulinate fluorescence cystoscopy in patients previously treated with intravesical bacille calmette-guerin. Journal of Urology 2011; 185(1): 100-101.

Thomas, K and O'Brien, T. Blue-sky thinking about blue-light cystoscopy. BJU International 2009; 104(7): 887-889.

Razzak, M. Bladder cancer: narrow-band imaging--improving urothelial carcinoma detection. Nature Reviews Urology 2012; 9(1): 3

Reason: Health economics

Malmstrom, PU et al. Fluorescence-guided transurethral resection of bladder cancer using hexaminolevulinate: analysis of health economic impact in Sweden. Scandinavian Journal of Urology & Nephrology 2009; 43(3): 192-198.

Reason: Project record

Hovi, S. Photodynamic diagnosis in bladder cancer detection and treatment (Project record). Health Technology Assessment Database. 2010;(3)

Rosette, J and Gravas, S. A multi-center, randomized international study to compare the impact of narrow band imaging versus white light cystoscopy in the recurrence of bladder cancer. Journal of Endourology 2010; 24(5): 660-661.

Evidence tables

Studies of PDD versus WLC from update search			
Study	**Participants**	**Tests**	**Outcomes summary**
Han 2010 Time period: Jan 2008 to Apr 2009 Country: China	Enrolled: 48; analysed: 48 No previous history of BC:NS; history of BC: NS Age (years): mean 59 range 36-86 Sex: M 40; F 8	Index test: PDD Agent: Pirarubicin hydrochloride Comparator: WLC 'Random' biopsies of normal appearing areas: yes (PDD and WLC)	Unit of analysis: Biopsy (n=238 PDD, n=225 WLC) Sensitivity: PDD 96%, WLC 82% Specificity: PDD 75%, WLC 80%
Kubin 2008 Time period: NS Country: Austria	Enrolled: 57; analysed: 57 No previous history of BC:NS; history of BC: NS Age (years): mean 73 range 38-97 Sex: M 47; F 10	Index test: PDD Agent: PVP-hypericin Comparator: WLC 'Random' biopsies of normal appearing areas: no	Unit of analysis: Biopsy (n=150) Sensitivity: PDD 95%, WLC 85% Specificity: PDD 53%, WLC 32%
Matsuyama 2009 Time period: NS Country: Japan	Enrolled: 20; analysed: 20 No previous history of BC: 9; history of BC: 11 Age (years): mean 69 range 56-86 Sex: M 17; F 3	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal appearing areas: yes (NS whether PDD or WLC or both)	Unit of analysis: Biopsy (n=60) Sensitivity: PDD 97%, WLC 74% Specificity: PDD 58%, WLC 85%
Lee 2012 Time period: 2010 Country: Korea	Enrolled: 30; analysed: 30 No previous of BC: 16; previous history of BC: 14 Age (years):mean 60 range 35-80 Sex: M 25; F 5	Index test: PDD Agent: HAL Comparator: WLC 'Random' biopsies of normal appearing areas: NR	Unit of analysis: Biopsy (n=134) Sensitivity: PDD 92%, WLC 81% Specificity: PDD 49%, WLC 58%

Study of health-related quality of life				
Study **Country**	**Study design**	**N patients**	**Patient characteristics**	**Outcome measures**
van der Aa (2008) Netherlands	Cross-sectional questionnaire	n=197 (732 questionnaires)	All non-muscle invasive urothelial cell carcinoma 75% M / 25% F Mean age=68 years	Pain, discomfort, overall burden, physical symptoms, general functioning, and satisfaction
Systematic review of diagnostic accuracy of WLC versus NBI				

Study	Methods	Included studies	Results	Additional comments
Zheng 2012 Systematic review	Assessed the test performance of narrow band imaging (NBI) compared with WLC in people suspected of new or recurrent bladder cancer, and included studies published in English and Chinese The quality of the included studies was assessed by the QUADAS tool.	8 included studies. All prospective. N patients ranged from 50 to 427. All studies report diagnostic accuracy for recurrent monitoring or for recurrent monitoring and early diagnosis. All considered good quality using QUADAS	Data analysis was conducted using the Meta-DiSc provided by the Cochrane Collaboration and a random effects model was used. SROC curves were drawn to describe the joint distribution of true positive and false positive rates Five studies (759 patients) were pooled for NBI in a patient level analysis. The pooled sensitivity and specificity of NBI were 94% (95% CI 91% to 96%) and 85% (95% CI 81% to 78%). Three studies (648 patients) were included in the pooled patient level estimates for WLC. The pooled sensitivity and specificity for WLC were 85% (95% CI 80% to 89%) and 87% (95% CI 83% to 90%). Four studies (341 patients, 1195 biopsies) were included in the pooled biopsy level analysis for NBI and WLC. The pooled sensitivity and specificity for NBI were 95% (95% CI 93% to 96%) and 55% (95% CI 50% to 59%). The pooled sensitivity and specificity for WLC were 75% (95% CI 72% to 78%) and 72% (95% CI 68% to 76%).	The authors reported significant heterogeneity among studies for NBI and WLC analysis, with I^2 values all above 75%, indicating high heterogeneity. Due to the low number of studies, a meta-regression and subgroup analyses could not be performed to identify the sources of heterogeneity.

HTA of PDD versus WLC

Study	Method	Included studies	Results	Additional comments
Mowatt et al (2010)	To be included, studies reporting test performance had to report the absolute numbers of true positives, false positives, false negatives and	27 studies (from 36 reports) were included in the HTA review **Characteristic** | **Number**	In both patient and biopsy based detection of bladder cancer PDD had a higher sensitivity but lower specificity than WLC. Five studies (370 patients) reported patient-based	Well-conducted review. Relevant to review question. HTA also included diagnostic

	true negatives, or provide information allowing their calculation. The reference standard for studies of diagnostic accuracy was histopathological examination of biopsied tissue. Studies reported as abstracts only were excluded.	**Patients** Enrolled Analysed **Suspicion of or previously diagnosed bladder cancer** Suspicion of BC Previously diagnosed BC Not reported **Age** Median (range) of means/medians (years) Not reported **Sex** Men Women Not reported 2949 2807 946 (41%) 1381 (59%) 481 67 (52-72) - 1647 (76%) 510 (24%) 656	detection. In the pooled estimates the sensitivity for PDD was 92% (95% CI 80% to 100%) compared with 71% (95% CI 49% to 93%) for WLC, whereas the specificity for PDD was 57% (95% CI 36% to 79%) compared with 72% (95% CI 47% to 96%) for WLC, with the CIs for the two techniques overlapping. A total of 14 studies (1746 patients) reported biopsy-based detection (number of biopsies: 8574 for PDD analysis, 8473 for WLC analysis). In the pooled estimates the sensitivity for PDD was 93% (95% CI 90% to 96%) compared with 65% (95% CI 55% to 74%) for WLC, whereas the specificity for PDD was 60% (95% CI 49% to 71%) compared with 81% (95% CI 73% to 90%) for WLC. The pair of CIs for both sensitivity and specificity did not overlap, providing evidence of a difference in diagnostic performance between the techniques.	accuracy of cytology and urinary biomarkers.

Systematic review of PDD versus WLC: Recurrence

Study	Method	Included studies	Results	Additional Comments
Burger et al (2013)	The meta-analysis focused on HAL, used as an addition to WLC. Included: prospective studies, patients with known or suspected NMIBC, used HAL cystoscopy, used histology to confirm the nature of lesions (true or false) Search conducted in July 2011 with no date restrictions.	Nine studies (10 papers) with 2212 patients were included. Individual patient data was obtained 5 studies excluded patients who had received chemotherapy or BCG in previous 3 months.	There were 188 out of 831 patients (22.6%) who had at least one additional Ta or T1 tumour that was only seen with blue light cystoscopy. The weighted patient level random-effects meta-analysis rate was 24.9% ((5% CI 0.184 to 0.328, p<0.001). The benefit was seen in all risk groups and in patients with primary and recurrent tumours. In patients who had at least one CIS lesion that was only seen with PDD and who had no CIS lesions seen with white light cystoscopy, the detection of patients with CIS lesions using HAL cystoscopy	Additional raw patient data was obtained from included studies.

			was significant (26.7%, 95% CI 0.183 to 0.371, p<0.001). Previous intravesical therapy had no effect on tumour detection. In all three studies included in the meta-analysis, HAL cystoscopy was associated with lower recurrence. The overall recurrence rate was 34.5% WLC versus 45.4% PDD (RR 0.76, 95% CI 0.63 to 0.92), in favour of HAL cystoscopy.	
Trial of NBI versus WLC: recurrence				
Study, Country	**Participants**	**Intervention/Comparison**	**Results**	**Additional comments**
Naselli (2011) Italy	Consecutive patients with overt or suspected bladder cancer between Aug 2009 to Sept 2010. Patients with invasive BC or absence of urothelial cancer after pathology or without follow-up were excluded.	Randomised to WLC (n=72) or NBI (n=76). No patients given immediate intravesical chemotherapy.	Primary endpoint: 1-yr intravesical recurrence. Median follow-up 11 mo (range 2-19). 12-month recurrence rate 32.9% (25/76) in the NBI group and 51.4% (37/72) in the WL group (RR 0.64, 95% CI 0.43 to 0.95).	Randomisation was centralised and used random table. Reasons for exclusion and withdrawal provided.

Health Economic Evidence

Health economic evidence was identified that covered this topic (endoscopic technique) as well as urinary biomarkers. The evidence is presented in a later section of this report where urinary biomarkers are discussed.

2.2 Transurethral surgical technique

2.2.1 Staging the primary tumour

Review question: Does the technique of transurethral surgery in new or recurrent bladder cancer influence outcomes?

Rationale

The accessibility of the bladder through the urethra means that bladder cancers may be treated by endoscopic excision. This transurethral resection may remove the cancer in its entirety or just confirm the nature of a cancer before further treatment. This topic will focus upon the practice of transurethral surgery for non-muscle invasive bladder cancers. Patients with these cancers often develop further bladder tumours following removal of their first lesion. These further tumours represent either residual disease (part of the previous cancer at the same location), recurrences related to the previous bladder cancer but spread to a different part of the bladder or new primary bladder cancers unrelated to the previous tumours.

The risk of further cancers within the bladder or of progression to invasive cancers reflects many factors. These may be related to the type of disease (e.g. low or high grade disease, tumours affecting single or multiple parts of the bladder), the patient (e.g. inherited genetic profile, continued or stopped carcinogen exposure) or the practice of transurethral surgery. Some surgeons feel that the practice of transurethral surgery needs to be standardised to all cancers, and include steps such as biopsying normal looking bladder wall to look for occult abnormal tissue. Others suggest that surgeons should be able to react to each tumour individually and tailor the practice of transurethral surgery accordingly. Case series and randomised trials have identified features related to the tumour and the surgeon that predict future outcomes.

This review will look at the aspects of surgical practice that may affect the subsequent behaviour of new or recurrent non-muscle invasive bladder cancers. This review should establish in which types of tumours the different techniques of transurethral surgery are recommended and identify standards defining good quality transurethral surgery.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with bladder cancer (new or recurrent)	Transurethral resection with muscle	Transurethral resection without muscle	• Recurrence • Progression • Residual tumour rate • Treatment-related morbidity • Health-related quality of life, inc. patient reported outcomes

METHODS

Information sources

A literature search was also performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

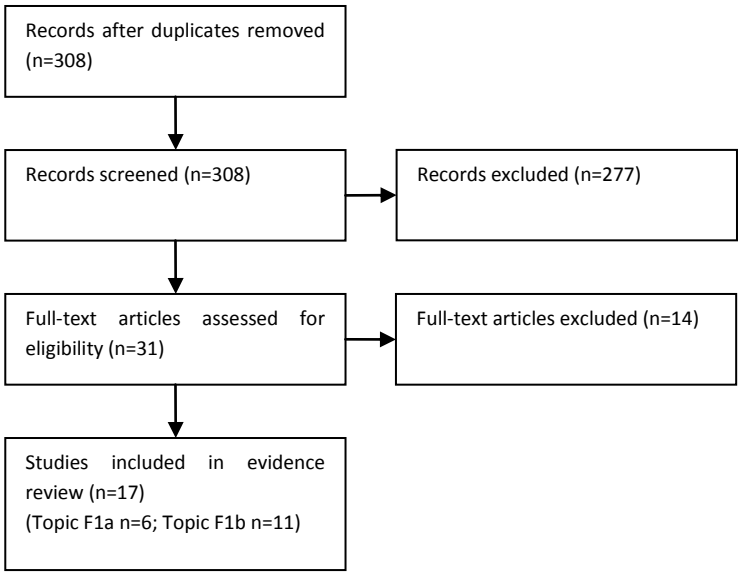
Data synthesis

Comparative studies reporting recurrence rates were pooled using RevMan and an overall risk ratio was calculated.

RESULTS

Result of the literature searches

Figure 9. Study flow diagram



Study quality and results

Low quality evidence was reported from six observational studies as assessed with GRADE. A summary of the included studies is provided in Table 16 and Figures 10-12.

Evidence statements

Three observational studies (972 patients) provided low quality evidence that the risk of recurrence at first follow-up cystoscopy was almost 50% lower for patients where detrusor muscle was present in their TUR specimen compared to those without detrusor muscle in their specimen (RR 0.54, 95% CI 0.46 to 0.64). One randomised trial (Kim *et al.*, 2012) provided very low quality evidence that continuing resection until the presence of muscle in the specimen is confirmed by intra-operative

pathology reduces rates of recurrence compared to a grossly complete resection, where only 65% of TUR specimens had muscle present (HR 0.28, 95% CI 0.13 to 0.63). One study (28 progression events, 245 patients) provided very low quality evidence that the presence of detrusor muscle in the TURBT specimen was not associated with disease progression after a median follow-up of 20.8 months (p=0.29) (Shoshany *et al.*, 2014). One study (128 patients) reported very low quality evidence that presence of detrusor muscle at the initial TURBT was associated with lower residual tumour rate at re-TURBT (20.9% versus 51.8%, RR 0.40, 95% CI 0.22 to 0.75). No evidence was reported for treatment-related morbidity or health-related quality of life.

Table 16. GRADE evidence profile: TURBT with detrusor muscle versus TURBT without detrusor muscle

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DM present	DM absent	Relative (95% CI)	Absolute	
Recurrence at first follow-up cystoscopy											
3[1]	observational studies	none	none	none	none	none	198/663 (29.9%)	152/309 (49.2%)	RR 0.54 (0.46 to 0.64)	226 fewer per 1000 (from 177 fewer to 266 fewer)	⊕⊕OO LOW
Recurrence (follow-up mean 16 months)											
1[2]	randomised trials	serious[3]	none	serious[4]	serious[5]	none	8/47 (17%)	23/50 (46%)	HR 0.28 (0.13 to 0.63)	302 fewer per 1000 (from 138 fewer to 383 fewer)	⊕OOO VERY LOW
Progression (follow-up median 20.8 months)											
1[6]	observational studies	none	none	none	serious[5]	none	Not reported separately – 28/245 (11%) in total progressed		DM not associated with progression, p=0.29	-	⊕OOO VERY LOW
Residual tumour rate (assessed with: re-TURBT)											
1[7]	observational studies	none	none	none	serious[5]	none	9/43 (20.9%)	44/85 (51.8%)	RR 0.40 (0.22 to 0.75)	311 fewer per 1000 (from 129 fewer to 404 fewer)	⊕OOO VERY LOW
Treatment-related morbidity											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Mariappan 2010, Mariappan 2012, Roupret 2012

[2] Kim 2012

[3] No intent-to-treat analysis in Kim (2012)

[4] 65% of patients in the comparison group had muscle in the TUR specimen. Hazard ratio relates to immediate 2nd TUR until MP present in specimen versus no immediate repeat TUR

[5] Low number of events reduces precision

[6] Shoshany 2012

[7] Huang 2012

Figure 10. Forest plot of presence versus absence of detrusor muscle in TUR specimen: Outcome, recurrence rate at first follow-up cystoscopy

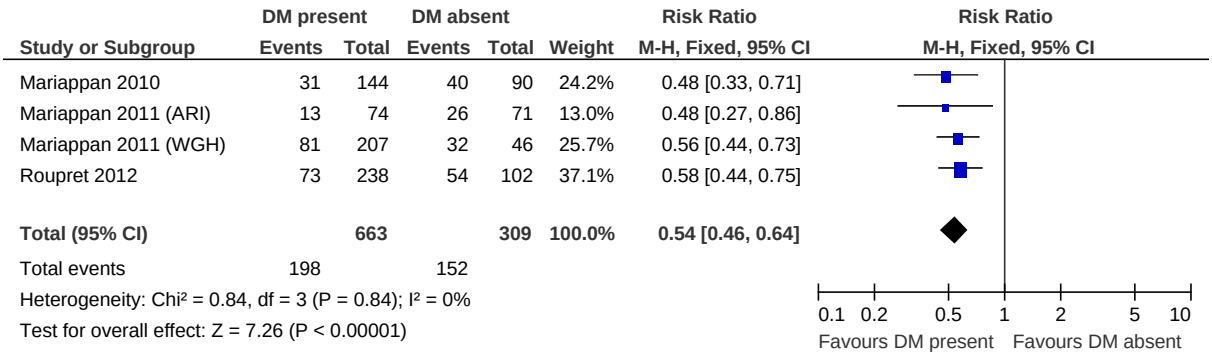


Figure 11. Forest plot of immediate 2nd TUR (DM in all specimens) versus no 2nd TUR (DM in 65% of specimens): Outcome, Recurrence

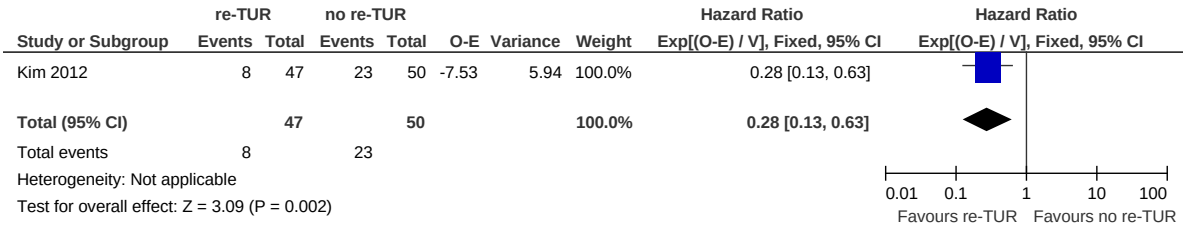
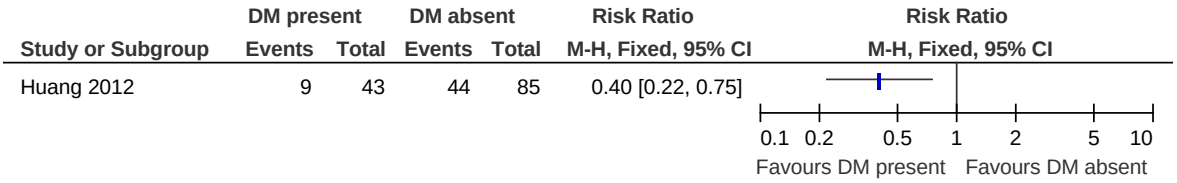


Figure 12. Forest plot of presence versus absence of detrusor muscle in TUR specimen: Outcome, residual tumour rate at re-TUR



References to included studies

Huang, J et al. Analysis of the absence of the detrusor muscle in initial transurethral resected specimens and the presence of residual tumor tissue. Urologia Internationalis 2012; 89(3): 319-325.

Kim, W et al. Value of immediate second resection of the tumor bed to improve the effectiveness of transurethral resection of bladder tumor. Journal of Endourology 2012; 26(8): 1059-1064.

Mariappan, P et al. Detrusor muscle in the first, apparently complete transurethral resection of bladder tumour specimen is a surrogate marker of resection quality, predicts risk of early recurrence, and is dependent on operator experience. European Urology 2010; 57(5): 843-849.

Mariappan, P et al. Good quality white-light transurethral resection of bladder tumours (GQ-WLTURBT) with experienced surgeons performing complete resections and obtaining detrusor

muscle reduces early recurrence in new non-muscle-invasive bladder cancer: validation across time and place and recommendation for benchmarking. BJU International 2012; 109(11): 1666-1673.

Roupret, M et al. The presence of detrusor muscle in the pathological specimen after transurethral resection of primary pT1 bladder tumors and its relationship to operator experience. Canadian Journal of Urology 2012; 19(5): 6459-6464.

Shoshany, O et al. Presence of detrusor muscle in bladder tumor specimens--predictors and effect on outcome as a measure of resection quality. Urologic Oncology 2014; 32(1): 40-22.

References to excluded studies (with reasons for exclusion)

Reason: not relevant to PICO

Alkhateeb S., F. Surgeon-volume and outcome relation in transurethral resection of bladder tumour (TURBT). Journal of Urology 2010; Conference(var.pagings): 4-e398.

Badalato, G et al. Does the presence of muscularis propria on transurethral resection of bladder tumour specimens affect the rate of upstaging in cT1 bladder cancer? BJU International 2011; 108(8): 1292-1296.

Chamie, K. The impact of accurate staging on bladder cancer survival: A process-outcomes link. Journal of Urology 2012; Conference(var.pagings): 4

Kumano, M. Significance of random bladder biopsies in patients undergoing transurethral resection of non-muscle invasive bladder cancer. Journal of Urology 2012; 187(4): E513

Huland, H et al. The value of histologic grading and staging, random biopsies, tumor and bladder mucosa blood group antigens, in predicting progression of superficial bladder cancer. European Urology 1984; 10(1): 28-31.

Ballon-Landa, EC. Quality of transurethral resection in patients with bladder cancer: A process-outcomes link. Journal of Clinical Oncology 2014; Conference(var.pagings): 4

Gan, C et al. Snapshot of transurethral resection of bladder tumours in the United Kingdom Audit (STUKA). BJU International 2013; 112(7): 930-935.

Reason: editorial comment/expert review

Daneshmand, S. The value of extended transurethral resection of bladder tumour (TURBT) in the treatment of bladder cancer. BJU International 2012; 110(2 Pt 2): E80

Sedelaar, JPM. Technique of TUR of Bladder Tumours: Value of Repeat TUR and Random Biopsies. EAU-EBU Update Series 2007; 5(4): 139-144.

Mostafid, H and Brausi, M. Measuring and improving the quality of transurethral resection for bladder tumour (TURBT). BJU International 2012; 109(11): 1579-1582.

Reason: non-comparative study, no specimens without DM

Richterstetter, M et al. The value of extended transurethral resection of bladder tumour (TURBT) in the treatment of bladder cancer. BJU International 2012; 110(2 Pt 2): E76-E79.

Reason: no assessment of presence of DM in specimen or random biopsies

Brausi, M et al. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. European Urology 2002; 41(5): 523-531.

Reason: foreign language

Fernandez Gomez, JM et al. [Significance of random biopsies of healthy mucosa in superficial bladder tumor]. [Spanish]. Archivos Espanoles de Urologia 2000; 53(9): 785-797.

Reason: duplicate of included study

Shoshany, O. Quality control in transurethral resection of bladder tumors (TURBT)-predicting presence of detrusor muscle (DM) in the surgical specimen and its impact on oncological outcomes. European Urology, Supplements 2012; Conference(var.pagings): 1-e1046a.

Evidence tables

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Mariappan 2010	Retrospective cohort study 2005-2006	N=398, 234 analysed for RR-FFC. Excluded MIBC, patients who missed f/up, non-TCC, and patients with incomplete resections. DM present in specimen n=241 (67.7%)	Mean age: 71.1 years Male: 254 (71%) Female: 102 (29%) Tumour size ≤3cm: 261 (73%) >3cm: 87 (25%) Unknown: 8 Tumour multiplicity Single: 301 (85%) Multiple: 55 (15%) Grade (WHO 1973) G1: 86 (24%) G2: 89 (25%) G3: 181 (51%) Primary stage Ta: 167 (47%) T1: 63 (18%) T2: 78 (22%) Tx: 48 (13.5%) Surgeon category Senior: 230 (65%) Junior: 118 (33%) Unknown: 8	New tumours that were completely resected using WLC and standard resection equipment. All patients had TUR and an intravesical instillation of MMC (40mg) within 24 hr of resection, unless bleeding or perforation. Attempted to obtain DM in all resections regardless of tumour appearance, by resecting the base separately if it was not resected with the main tumour. Patients with G3 and/or T1 disease had re-TURBT within 6wk. All other patients had cystoscopy at 3 mo following first TURBT, with recurrence confirmed by biopsy/resection. Of those included in RR-FFC analysis, 158 patients had first f/up cystoscopy at 3 mo, 76 had re-TURBT.	DM present vs. DM absent Univariate and multivariate analysis used to assess associations between variables	N/A	RR-FFC: recurrence at first follow-up cystoscopy Overall RR-FFC = 30.3% (n=71) Tumour stage T1, absence of DM, resection by junior surgeons were independent predictors of RR-FFC. RR-FFC: 44.4% DM absent vs. 21.7% DM present (OR 2.9, 95% CI 1.6-5.4)	None	

<table>
<tr><th>Study</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Mariappan 2011</td>
<td>Retrospective cohort study

WGH cohort 1978-1984 (N=341)
ARI cohort 2005-2006 (N=225)

Excluded MIBC, patients who missed f/up, non-TCC, and patients with incomplete resections.</td>
<td>N=473 suitable for demographic and DM status description</td>
<td>
<table>
<tr><th></th><th>WGH cohort n (%)</th><th>ARI cohort n (%)</th></tr>
<tr><td>Mean age</td><td>64.8 yrs</td><td>70 yrs</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Male</td><td>224 (73)</td><td>NR</td></tr>
<tr><td>Female</td><td>84 (27)</td><td>NR</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Tumour size</td><td></td><td></td></tr>
<tr><td>≤3cm</td><td>22 (72)</td><td>NR</td></tr>
<tr><td>>3cm</td><td>86 (28)</td><td>NR</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Tumour multiplicity</td><td></td><td></td></tr>
<tr><td>Single</td><td>201 (65)</td><td>NR</td></tr>
<tr><td>Multiple</td><td>107 (35)</td><td>NR</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Grade (WHO 1973)</td><td></td><td></td></tr>
<tr><td>G1</td><td>128 (42)</td><td>58 (35)</td></tr>
<tr><td>G2</td><td>36 (12)</td><td>66 (40)</td></tr>
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<tr><td>Junior</td><td>76 (52)</td></tr>
<tr><td>unknown</td><td>19</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>DM (NMIBC) only</td><td></td><td></td></tr>
<tr><td>Present</td><td>250 (81)</td><td>79 (48)</td></tr>
<tr><td>absent</td><td>58 (19)</td><td>86 (52)</td></tr>
</table>
</td>
<td>In the WGH cohort intravesical chemo and re-TURBT were not standard treatments. All had 1st check cystoscopy under general anaesthetic at 3mo.

ARI cohort: All patients had TUR and an intravesical instillation of MMC (40mg) within 24 hr of resection, unless bleeding or perforation. Attempted to obtain DM in all resections regardless of tumour appearance, by resecting the base separately if it was not resected with the main tumour.
Patients with G3 and/or T1 disease had re-TURBT within 6wk. All other patients had cystoscopy at 3 mo following first TURBT, with recurrence confirmed by biopsy/resection.</td>
<td>DM present vs. DM absent

Univariate and multivariate analysis used to assess associations between variables</td>
<td>N/A</td>
<td>RR-FFC: recurrence at first follow-up cystoscopy

WGH cohort (n=253):
Overall RR-FFC = 44.7%

RR-FFC: 69.6% DM absent vs. 39.1% DM present (OR 3.6, 95% CI 1.7-7.5)

Tumour multiplicity, absence of DM, and stage were independent predictors of RR-FFC.

ARI cohort (n=145):
Overall RR-FFC = 26.9%

RR-FFC: 42.6% DM absent vs. 17.6% DM present (OR 2.7, 95% CI 1.2-6.3)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Roupret 2012</td>
<td>Retrospective cohort study

2002-2009</td>
<td>N= 340 pT1 patients</td>
<td>
<table>
<tr><td>Median age</td><td>69 years</td></tr>
<tr><td>Age range</td><td>33 to 98</td></tr>
<tr><td>Male</td><td>254 (79%)</td></tr>
<tr><td>Female</td><td>68 (21%)</td></tr>
<tr><td></td><td></td></tr>
</table>
</td>
<td>DM absent in 102 (30%) specimens. TURBTs systematically performed using white-light cystoscopy. Intravesical</td>
<td>DM present vs. DM absent</td>
<td>Not reported</td>
<td>RR-FFC: recurrence at first follow-up cystoscopy
30.7% (n=73) DM present versus 52.9% (n=54) DM absent (OR 2.33, 95% CI 1.45-</td>
<td>N/a</td>
<td></td>
</tr>
</table>

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			Tumour size <3cm 101 (27%) >3cm 239 (73%) Grade Low 17 (5%) High 323 (95%) Primary stage T1x 33 (10%) T1a 183 (54%) T1b 124 (36%) Surgeon category Senior 103 (30%) Junior 237 (70%) Associated CIS 59 (17%)	chemotherapy was not routinely administered postoperatively. In case of multifocal tumours, only the largest one was considered in this study. pT1 tumours were subdivided into 2 groups: those with (T1b) or without tumour invasion of the muscularis mucosa layer of the lamina propria (pT1a).			3.74)		
Huang 2012	Retrospective cohort study 2008-2011	N=216 primary tumours. Excluded incomplete resections, MIBC, non-TCC.	<table><tr><td></td><td>Total n=216</td><td>Re-TUR n=126</td></tr><tr><td>Median age</td><td>69±5.6 yrs</td><td>NR</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Male</td><td>173 (80%)</td><td>NR</td></tr><tr><td>Female</td><td>43 (20%)</td><td>NR</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Tumour size</td><td></td><td></td></tr><tr><td><3cm</td><td>156 (72%)</td><td>91 (72%)</td></tr><tr><td>≥3cm</td><td>52 (24%)</td><td>27 (21%)</td></tr><tr><td>Unknown</td><td>8 (4)</td><td></td></tr><tr><td></td><td></td><td></td></tr><tr><td>Grade</td><td></td><td></td></tr><tr><td>G1</td><td>102 (47%)</td><td>52 (41%)</td></tr><tr><td>G2</td><td>59 (27%)</td><td>33 (26%)</td></tr><tr><td>G3</td><td>55 (26%)</td><td>51 (40%)</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Primary stage</td><td></td><td></td></tr><tr><td>Ta</td><td>104(48%)</td><td>52 (41%)</td></tr><tr><td>T1</td><td>47 (22%)</td><td>47 (37%)</td></tr><tr><td>T2</td><td>30 (14%)</td><td>n/a</td></tr></table>	Primary tumours that were determined to have been completely resected. Standard practice to attempt a thorough and complete resection including DM in all resections. Resect base of tumour separately if not with main tumour. G3 and/or T1 disease and whose specimens did not contain DM underwent an early TURBT within 2-6wks of 1st TURBT. All 2nd resections performed by senior surgeons. 128 patients were re-resected. 2 patients with unclear surgeon status excluded from analysis.	DM absent vs. DM present	n/a	Residual tumour rate at re-TURBT (n=128): 51.8% (44/85) DM absent vs. 20.9% (9/43) DM present (multivariate OR 15.537, 95% CI 2.814 to 85.789)	n/a	Not stated how many patients underwent re-TUR due to lack of DM in 1st TUR or due to G3/T1 disease

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			Tx 35 (16%) n/a Single 165 (76%) 95 (75%) Multiple 51 (24%) 33 (26%) Tumour location Posterior 46 (21%) 19 (15%) Lateral 134 (62%) 85 (67%) Dome/anterior 30 (14%) 17 (13%) Unspecified 6 (3%) Surgeon category Senior 120 (56%) 44 (35%) Junior 94 (44%) 82 (65%) DM status Present 110 (51%) Absent 106 (49%)						
Shoshany 2014	Retrospective cohort study 2008-2009	N=332 with complete resection of tumour Excluded restaging TURBT. All TURBT performed with WLC	Mean age 73 Male 266 (80%) female 66 (20%) Bladder cancer history 190 (57%) Prior IVT 121 (36%) Ta 160 (60%) T1 81 (30%) T2 20 (7%) Tx 8 (3%) High grade 159 (58%) <3cm 272 (82%) mulitfocal 148 (45%)	All had complete resection of tumour. Specimens analysed by 3 pathologists.	DM present vs. DM absent	Median 20.8 mo	DM present in 265/332 (79%) specimens. Of 253 with TCC and NMIBC, 17 lost to follow-up, 9 unable to have cystoscopic surveillance, 6 offered RC. 101 patients had recurrence 28 progressed The presence of DM in specimen was not associated with disease recurrence (p=0.65) or progression (p=0.29)	Not reported	
Kim 2012 Korea	Randomised clinical trial	126	Inclusion criteria: major axis of tumour > 2cm, 2 or more tumours, patients had previous intermediate or high risk tumours, the tumours were non-papillary and the tumours had a broad based shape Patients who underwent cystectomy (19 T2 and 6 T1G3) were excluded from	Second TURB done immediately after first TURB was grossly complete. TURB was repeated until MP in specimen was confirmed by intra-TUR frozen biopsy results.	Initial TURB only – stopped when grossly complete. 65% had MP in TURB specimen	Mean follow-up was 16 months for the repeat TURB group	Tumour recurrence (2nd TURB vs. no 2nd TURB) 8/47 vs. 23/50; HR=0.274 (95%C.I. 0.112 to 0.669) For high risk group (T1 or TaG3) 2yr recurrence rates were 27.5% versus 58% (P=0.015, log rank test)	No competing financial interests declared	No intention to treat analysis – 19 T2 and 6 T1G3 excluded from

<table>
<tr><th>Study</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>the analysis.
<table>
<tr><th rowspan="2">Group</th><th colspan="4">Tumour stage</th></tr>
<tr><th>Ta</th><th>T1</th><th>T2</th><th>CIS</th></tr>
<tr><td>Repeat TURB</td><td>32</td><td>17</td><td>12</td><td>2</td></tr>
<tr><td>No repeat</td><td>32</td><td>18</td><td>12</td><td>1</td></tr>
</table>
<table>
<tr><th rowspan="2">Group</th><th colspan="2">Grade</th></tr>
<tr><th>Low</th><th>High</th></tr>
<tr><td>Repeat TURB</td><td>25</td><td>38</td></tr>
<tr><td>No repeat</td><td>31</td><td>32</td></tr>
</table></td><td></td><td></td><td>and 17 months for the non-repeat group.</td><td>For low risk group 2yr recurrence rates were 50.1% versus 52.6% (P=0.015, log rank test)
Cystectomy within 3 months after TUR (2nd TURB vs. no 2nd TURB)
12/63 versus 13/63</td><td></td><td>analysis due to cystectomy. Sub optimal first TURB in the comparison group? Unclear whether all were high risk NMIBC</td></tr>
</table>

2.2.2 Assessing normal looking bladder

Review question: Does random biopsy affect outcomes in people with non-muscle invasive bladder cancer?

Rationale

This review will look at the aspects of surgical practice that may affect the subsequent behaviour of new or recurrent non-muscle invasive bladder cancers. This review should establish in which types of tumours the different techniques of transurethral surgery are recommended and identify standards defining good quality transurethral surgery.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with NMIBC (new or recurrent)	Transurethral resection with random biopsies	Transurethral resection without random biopsies	• Recurrence • Progression • Residual tumour rate • Treatment-related morbidity • Health-related quality of life, inc patient reported outcomes

METHODS

Information sources

A literature search was also performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

Data synthesis

Studies reporting the rate of positive random biopsies were summarised as a marker of residual tumour rate. Risk ratios were calculated for the recurrence data from comparative studies.

RESULTS

Result of the literature searches

See flow diagram in Figure 9 above.

Study quality and results

Very low quality evidence from 11 observational studies was reported as assessed with GRADE. The evidence is summarised in Table 17-18.

Evidence statements

One observational study reported very low quality evidence on the recurrence rate at first follow-up cystoscopy (Thortenson *et al.*, 2010). In patients with NMIBC in whom random bladder biopsies were

performed (n=260), 40.8% had recurrence at first-follow-up cystoscopy, compared with 21.4% of those who did not undergo random biopsies (n=142). Recurrence rate during a median follow-up of 54 months for those with and without random biopsies was 68.2% and 51.4%, respectively (RR 1.14, 95% CI 0.96 to 1.36) in favour of no random biopsies. The rate of positive random biopsies was reported in 11 studies (very low quality evidence) which varied from 4.3% (van der Meijden *et al.*, 1999) to 40% (Librenjak *et al.*, 2010) across studies. Overall 13.6% (580/1420) of random biopsies were positive for pathological findings. The random biopsy procedure varied across studies. For example, Librenjak *et al.* (2010) took biopsies close to the resected tumour edge, whereas most other studies took random biopsies from normal-appearing urothelium at pre-specified sites e.g. bladder neck, trigone, right and left lateral walls, posterior and anterior wall. The studies also varied in the definition of a positive random biopsy, which has an effect on the positive biopsy rate reported. The rate of positive biopsies generally increased with increasing stage and grade of the primary tumour. One study (Librenjak *et al.*, 2010) reported that taking biopsy specimens from normal-appearing urothelium did not prolong the time of resection, neither was it associated with more complications such as bleeding and bladder rupture. Progression and health-related quality of life were not reported in the evidence.

Table 17. GRADE evidence profile: Random biopsies versus no random biopsies

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Random biopsy	No random biopsy	Relative (95% CI)	Absolute	
Recurrence at first check-up											
1[1]	observational studies	none	none	none	serious[2]	none	104/255 (40.8%)	30/140 (21.4%)	RR 1.44 (1.03 to 2.01)	94 more per 1000 (from 6 more to 216 more)	⊕OOO VERY LOW
Recurrence at first check-up - PUNLMP											
1[1]	observational studies	none	none	none	serious[2]	none	0/10 (0%)	0/24 (0%)	not pooled	not pooled	⊕OOO VERY LOW
Recurrence at first check-up - TaG1-G2											
1[1]	observational studies	none	none	none	serious[2]	none	51/147 (34.7%)	20/95 (21.1%)	RR 1.65 (1.05 to 2.58)	137 more per 1000 (from 11 more to 333 more)	⊕OOO VERY LOW
Recurrence at first check-up - TaG3 and T1G1-G3											
1[1]	observational studies	none	none	none	serious[2]	none	53/98 (54.1%)	10/21 (47.6%)	RR 1.14 (0.7 to 1.84)	67 more per 1000 (from 143 fewer to 400 more)	⊕OOO VERY LOW
Recurrence during follow-up (follow-up median 54 months)											
1[1]	observational studies	none	none	none	serious[2]	none	174/255 (68.2%)	72/140 (51.4%)	RR 1.14 (0.96 to 1.36)	72 more per 1000 (from 21 fewer to 185 more)	⊕OOO VERY LOW
Recurrence during follow-up - PUNLMP (follow-up median 54 months)											
1[1]	observational studies	none	none	none	serious[2]	none	3/10 (30%)	2/24 (8.3%)	RR 3.6 (0.71 to 18.37)	217 more per 1000 (from 24 fewer to 1000 more)	⊕OOO VERY LOW
Recurrence during follow-up - TaG1-G2 (follow-up median 54 months)											
1[1]	observational studies	none	none	none	serious[2]	none	95/147 (64.6%)	56/95 (58.9%)	RR 1.1 (0.89 to 1.35)	59 more per 1000 (from 65 fewer to 206 more)	⊕OOO VERY LOW
Recurrence during follow-up - TaG3 and T1G1-G3 (follow-up median 54 months)											
1[1]	observational studies	none	none	none	serious[2]	none	76/98 (77.6%)	14/21 (66.7%)	RR 1.16 (0.84 to 1.6)	107 more per 1000 (from 107 fewer to 400 more)	⊕OOO VERY LOW
Progression											
0	No evidence available										
Residual tumour rate (assessed with: Positive random biopsy)											
11[3]	observational studies	serious[4]	none	none	none	none	580/4270 (13.6%)	N/A	-	-	⊕OOO VERY LOW
Treatment-related morbidity											
1[5]	observational studies	serious[6]	none	none	serious[2]	none	R biopsies not associated with more complications e.g. bleeding			-	⊕OOO VERY LOW
Health-related quality of life											

0	No evidence available										

[1] Thortenson 2010 (excluding patients with T2+ primary tumour); [2] Low number of events/small sample size limits precision; [3] Thortenson 2010; Librenjak 2010; Cohen 2010; May 2003 ; Gorgus 2002; Taguchi 1998; Mufti 1992; Ozen 1983; Vicente-Rodriguez 1987; Van der Meijden 1999; Witjes 1992; [4] All non-comparative retrospective cohort studies. Definitions of positive random biopsy and patient selection for random biopsy varied across studies; [5] Librenjak 2010; [6] Number of patients and events not reported for treatment-related morbidity

Table 18. Rate of positive random biopsy by study

Study	Pathological findings on random biopsy, n (%)	Definition of positive random biopsy	CIS on random biopsy, n (%)
Thortenson 2010	47/326 (14%)	Concomitant CIS	47/326 (14%)
Librenjak 2010	92/230 (40%)	Tumour tissue, Tis, dysplasia	31/230 (13.5%)
Cohen 2010	3/64 (4.7%)	All Ta	
May 2003	128/1033 (12.4%)	Tis, Ta, T1	74/1033 (7.2%)
Gorgus 2002	7/84 (8.3%)	CIS, dysplasia	4/84 (4.8%)
Taguchi 1998	20/83 (24.1%)	CIS, dysplasia	12/83 (14.5%)
Mufti 1992	27/115 (23%)	CIS, dysplasia, tumour	5/115 (4.3%)
Ozen 1983	67/94 (71%) *	Dysplasia, hyperplasia, CIS, squamous metaplasia	
Vicente-Rodriguez 1987	52/314 (16.6%)	CIS	52/314 (16.6%)
Van der Meijden 1999 (EORTC 30863)	17/393 (4.3%)	CIS, Ta, ≥T1	6/393 (1.5%)
Van der Meijden 1999 (EORTC 30911)	70/602 (11.6%)	Ta, T1	
Witjes 1992	217/1026 (21.2%)	Dysplasia, CIS	
Total	**580/4270 (13.6%)**		**231/2578 (9%)**

References to included studies

Cohen, M. Is there a role for random biopsies of the bladder on the cystoscopy following intravesical BCG induction course. European Urology, Supplements 2010; Conference(var.pagings): 2

Gogus, C et al. The significance of random bladder biopsies in superficial bladder cancer. International Urology & Nephrology 2002; 34(1): 59-61.

Librenjak, D et al. Biopsies of the normal-appearing urothelium in primary bladder cancer. Urology annals 2010; 2(2): 71-75.

May, F et al. Significance of random bladder biopsies in superficial bladder cancer. European Urology 2003; 44(1): 47-50.

Mufti, GR and Singh, M. Value of random mucosal biopsies in the management of superficial bladder cancer. European Urology 1992; 22(4): 288-293.

Ozen, H et al. Biopsy of apparently normal bladder mucosa in patients with bladder carcinoma and its prognostic importance. International Urology & Nephrology 1983; 15(4): 327-332.

Taguchi, I et al. Clinical evaluation of random biopsy of urinary bladder in patients with superficial bladder cancer. International Journal of Urology 1998; 5(1): 30-34.

Thorstenson, A et al. Diagnostic random bladder biopsies: reflections from a population-based cohort of 538 patients. Scandinavian Journal of Urology & Nephrology 2010; 44(1): 11-19.

van der Meijden, A et al. Significance of bladder biopsies in Ta,T1 bladder tumors: a report from the EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC-GU Group Superficial Bladder Committee. European Urology 1999; 35(4): 267-271.

Vicente-Rodriguez, J et al. Value of random endoscopic biopsy in the diagnosis of bladder carcinoma in situ. European Urology 1987; 13(3): 150-152.

Witjes, JA. Random bladder biopsies and the risk of recurrent superficial bladder cancer: A prospective study in 1026 patients. World Journal of Urology 1992; 10(4): 231-234.

References to excluded studies (with reasons for exclusion)

See excluded studies for previous topic.

Evidence tables

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Thorstenson 2010	Retrospective cohort 1995-1996	N=527 without primary CIS	PUNLMP 34 (6.3%) pTaG1-G2 243 (45.2%) pTaG3 & pT1G1-G3 125 (23.2%) pT2+ 125 (23.2%) 326/527 (62%) had R biopsies at initial TURBT	In all patients the first treatment was TURBT. R biopsies recommended in all patients but decision left to treating urologist. R biopsies taken adjacent to tumour, the right and left lateral walls, the trigone and the posterior bladder wall. Biopsies from prostatic urethra not generally taken. R biopsies classified as normal or concomitant CIS if CIS found in any specimen	R biopsy vs. No R biopsy	Median 54 mo. Max 80 mo	Rate of concomitant CIS: 0/10 (0%) PUNLMP 3/147 (2%) pTaG1-G2 23/103 (22%) pTaG3 and pT1G1-G3 21/66 (31.8%) pT2+ Intravesical recurrence at first check-up: PUNLMP= 0 TaG1-G2 – R biopsy 95/147 (65%), no Rb 56/95 (59%) pTaG3 and pT1G1-G3 – R biopsy 53/98 (54%), no Rb 10/21 (48%) pT2+ N/A Any intravesical recurrence during follow-up: PUNLMP – R biopsy 3/10 (30%), no Rb 2/24 (8%) T1G1-G2 – R biopsy 95/147 (65%), no Rb 56/95 (59%) TaG3 and pT1G1-G3 – R biopsy 76/98 (78%), no Rb 14/21 (67%) pT2+ N/A Death due to bladder cancer in pTaG3 or pT1G1-G3, no R biopsy versus R biopsy HR =2.5 (95% CI 1.1-5.6)	None	
Librenjak 2010	Cohort study appears prospective 2001-2008	N=230 with primary bladder cancer	176 (77%) Male, mean age 67±11 years 54 (23%) Female, mean age 68±11 years Ta 131 (57%) T1 61 (27%) T2 38 (17%) G1 88 (38%) G2 59 (26%) G3 83 (36%)	During initial TURBT, R biopsies taken from normal-appearing urothelium at edge of resected tumour. Positive findings of biopsy specimen tumour tissue, tumour in situ (Tis), and dysplasia. Resected the surrounding urothelium without tumours and biopsy specimens from the normal-appearing mucosa 6mm away from resection edge, which was the diameter of the resection loop.	n/a	n/a	Positive R biopsy (tumour tissue, Tis, and dysplasia): Total: 92/230 (40%) pathological findings in normal-appearing urothelium – 42 (46%) tumour tissue, 31 (34%) Tis, 19 (21%) dysplasia G1 16/88 (18%) G2 19/59 (33%) G3 57/83 (69%) TaG1 16/84 (19%) Ta G2 11/38 (29%) TaG3 5/9 (56%)	None	

<table>
<tr><th>Study</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Solitary</td><td>156 (68%)</td></tr>
<tr><td>Multiple</td><td>74 (32%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td><2cm</td><td>85 (37%)</td></tr>
<tr><td>2-5cm</td><td>88 (38%)</td></tr>
<tr><td>>5cm</td><td>57 (25%)</td></tr>
</table>
</td><td></td><td></td><td></td><td>T1G1 0 (0%)
T1G2 8/23 (35%)
T1G3 22/38 (58%)
<table>
<tr><td>TUR stage</td><td colspan="4">R biopsy result</td></tr>
<tr><td></td><td>TT*</td><td>Tis</td><td>D*</td><td>total</td></tr>
<tr><td>Ta (131)</td><td>17
13%</td><td>8
6%</td><td>7
5%</td><td>32
24%</td></tr>
<tr><td>T1 (61)</td><td>10
17%</td><td>11
18%</td><td>9
15%</td><td>30
50%</td></tr>
<tr><td>T2 (38)</td><td>15
39%</td><td>12
32%</td><td>3
8%</td><td>30
79%</td></tr>
<tr><td>Total (230)</td><td>42
46%</td><td>31
34%</td><td>19
21%</td><td></td></tr>
</table>
*TT=Tumour tissue, D=Dysplasia

Treatment-related morbidity: R biopsy not associated with more complications such as bleeding and bladder rupture</td><td></td><td></td></tr>
<tr><td>Cohen 2010</td><td>Retrospective cohort study

1998-2007</td><td>N=207 NMIBC patients treated with induction BCG</td><td>108 (52.2%) had normal biopsy results and 99 (47.8%) had abnormal/suspicious results on the cystoscopy following BCG therapy.</td><td>R biopsies performed in 64/108 (59%) of normal appearing bladders.</td><td>n/a</td><td>n/a</td><td>Positive R biopsies: 3/64 (4.7%)
2 Ta low grade, 1 Ta high grade, with normal concomitant urine cytology.</td><td>Not reported</td><td>Abstract only</td></tr>
<tr><td>May 2003</td><td>Cohort study appears prospective

1998-2000</td><td>N=1033 consecutive patients with Ta, T1 or Tis. Patients with small, primary, singular tumours (≤1cm) were excluded from random biopsies.</td><td>
<table>
<tr><td>pTa</td><td>755 (73%)</td></tr>
<tr><td>pTis</td><td>37 (4%)</td></tr>
<tr><td>pT1</td><td>227 (22%)</td></tr>
<tr><td>PT0</td><td>14 (1%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>G1</td><td>346 (34%)</td></tr>
<tr><td>G2</td><td>479 (47%)</td></tr>
<tr><td>G3</td><td>194 (19%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Multiple</td><td>423 (41%)</td></tr>
<tr><td>Recurrent</td><td>465 (45%)</td></tr>
</table>
</td><td>Patients with Ta, T1 or Tis at increased risk for recurrence underwent multiple biopsies from normal-appearing urothelium after TUR. R biopsies with a cold punch at the time of TURBT. Biopsies explored the bladder floor, right wall, left wall, dome, posterior wall, and prostatic urethra (in males) or bladder neck (in females)</td><td>n/a</td><td>n/a</td><td>Result of R biopsy:
No tumour n=905 (87.6%). 128/1033 (12.4%) showed urothelial bladder cancer in R biopsy material
<table>
<tr><td>TUR stage</td><td colspan="4">R biopsy result</td></tr>
<tr><td></td><td>Tis</td><td>Ta</td><td>T1</td><td>total</td></tr>
<tr><td>Ta (755)</td><td>25</td><td>26</td><td>2</td><td>53, 7%</td></tr>
<tr><td>T1 (227)</td><td>31</td><td>5</td><td>7</td><td>44*, 19%</td></tr>
<tr><td>Tis (37)</td><td>13</td><td>2</td><td>2</td><td>17, 46%</td></tr>
<tr><td>T0 (14)</td><td>5</td><td>8</td><td>1</td><td>14, 100%</td></tr>
</table>
</td><td>Not reported</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Total (1033)</td><td>74
7%</td><td>41
4%</td><td>12
1%</td><td>128,
12.4%</td></tr>
</table>
*One pT2 lesion was found in a patient with primary T1 tumour

Upstaging of the primary resected tumour in 75 patients (7%)</td><td></td><td></td></tr>
<tr><td>Gogus 2002</td><td>Cohort study appears prospective</td><td>N=84 with Ta, T1 tumours</td><td>
<table>
<tr><td>Mean age</td><td>60 years</td></tr>
<tr><td>Age range</td><td>31-88</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Male</td><td>52 (62%)</td></tr>
<tr><td>Female</td><td>32 (38%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>pTa</td><td>40 (48%)</td></tr>
<tr><td>pT1</td><td>44 (52%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>G1</td><td>26 (31%)</td></tr>
<tr><td>G2</td><td>44 (52%)</td></tr>
<tr><td>G3</td><td>14 (17%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Solitary</td><td>49 (58%)</td></tr>
<tr><td>Multiple</td><td>35 (42%)</td></tr>
</table>
</td><td>R biopsies from normal appearing mucosa performed after TURBT, taken from right and left bladder walls, anterior and posterior walls, dome, trigone, and prostatic urethra with cold cup technique.</td><td>N/a</td><td>n/a</td><td>Results of R biopsy:
7/84 (8.3%) had urothelial abnormalities (CIS or dysplasia). No pathology in 77/84 patients.

<table>
<tr><td></td><td>+ve Rb</td><td>Dyspla-sia</td><td>CIS</td></tr>
<tr><td>Ta (40)</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>T1 (44)</td><td>7
15.9%</td><td>3
6.8%</td><td>4
9.1%</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>G1 (26)</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>G2 (44)</td><td>2
4.5%</td><td>2
4.5%</td><td>0</td></tr>
<tr><td>G3 (14)</td><td>5
36%</td><td>1
7%</td><td>4
29%</td></tr>
</table>
</td><td>N/a</td><td></td></tr>
<tr><td>Taguchi 1998</td><td>Cohort study appears prospective

1990-1996</td><td>N=83 with NMIBC (all TCC)</td><td>
<table>
<tr><td>Mean age</td><td>65.6 yrs</td></tr>
<tr><td>Age range</td><td>39-91</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Male</td><td>74 (89%)</td></tr>
<tr><td>Female</td><td>9 (11%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>pTa</td><td>51 (61%)</td></tr>
<tr><td>pT1</td><td>32(39%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>G1</td><td>32 (39%)</td></tr>
<tr><td>G2</td><td>39 (47%)</td></tr>
<tr><td>G3</td><td>12 (14%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Solitary</td><td>39 (47%)</td></tr>
<tr><td>Multiple</td><td>44 (53%)</td></tr>
<tr><td></td><td></td></tr>
</table>
</td><td>83 patients treated with TURBT underwent R biopsy in 6 sites: bladder neck, trigone, right and left lateral walls, posterior wall and anterior wall, with endoscopically normal mucosal findings.
Random biopsies classified as no malignancy (negative biopsy) and CIS and/or dysplasia (positive biopsy).
After TURBT BCG given in 18 patients with +ve biopsy or pT1 and/or G3 tumours. For tumours other than G3 or with –ve biopsy 4’-epiadriamycine (n=22), or doxorubicin (n=24) was given. 19 patients with T1G1 solitary tumour and negative biopsy did not receive intravesical instillation.</td><td>n/a</td><td>Median 18 mo (3-61)</td><td>Incidence of positive R biopsy:
n=20/83 (24.1%), CIS (n=12, 14.5%), dysplasia (n=8, 9.6%)

<table>
<tr><td></td><td>+ve Rb</td><td>Dysp lasia</td><td>CIS</td></tr>
<tr><td>Non-papillary and/or >3 tumours</td><td>14
42%</td><td>6
18%</td><td>8
24%</td></tr>
<tr><td>Papillary and 1 or 2 tumours</td><td>6
12%</td><td>2
4%</td><td>4
8%</td></tr>
<tr><td>Total (n=83)</td><td>20
24%</td><td>8
9.6%</td><td>12
14.5%</td></tr>
</table>

Recurrence detected in 21/83 (25.3%)</td><td>n/a</td><td></td></tr>
</table>

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			<10mm: 18 (22%) ≥10mm: 65 (78%)				patients. Median interval between surgery and recurrence=9 months (range, 4 to 26 mo). Recurrence in 15/63 (23.8%) with negative R biopsy, 3/8 (37.5%) with dysplasia, and 3/12 (25%) with CIS. No significant difference in disease-free survival according to biopsy result. No patient with positive biopsy showed progression.		
Mufti 1992	Retrospective cohort study 1983-1990	N=115. Excluded previous UUT and either G3 or associated carcinoma of prostate	Mean age 61, range 31-86 years Males: females, 3:1 72 (67%) Grade 1 38 (33%) Grade 2	All tumours resected endoscopically. R mucosal biopsies obtained from normal-looking mucosa; one each from posterior, right lateral, left lateral and anterior wall. Either at same time as resection of primary tumour or during course of one of the f/up cystoscopies when bladder was free of visible disease (interval between initial resection and R biopsies was at least 3 mo). No biopsies taken closer than 1cm from the tumour. Patients followed up at regular intervals. Intravesical chemotherapy started if new tumours became sufficiently frequent and numerous that they could not be controlled by endoscopic treatment alone, or if biopsies revealed CIS.	n/a	Mean 3.3 yrs, max 6.5 yrs	Rate of epithelial abnormalities in R biopsies: 27/115 (23%) +ve Rb G1 (77): 15 (19%) G2 (38): 12 (33%) Single (88): 14 (16%) Multiple (27): 13 (48%) Total (115): 27 (23%) N (% of 27 abnormal Rb) Dysplasia: 17 (63%) CIS: 5 (19%) PT1 G1 TCC: 3 (11%) pT1 G2 TCC: 2 (7%)	n/a	
Ozen 1983	Cohort study appears prospective 1980-1981	N=25	Mean age 62 years (range, 58-81) G1: 3 (12%) G2: 12 (48%) G3: 3 (12%) G4: 7 (28%) T1: 6 (24%) T2-T4: 19 (76%)	In patients with histologically confirmed TCC, 100 cold cup biopsies were obtained from normal-looking mucosa at preselected sites – ureteral orifice, midline posteriorly, and adjacent to the tumour. 6 biopsies were found to be insufficient	n/a	9 to 24 mo	94 biopsies from 25 patients (rate per patient not reported): Dysplasia 40.49% Hyperplasia 17.35% Squamous metaplasia 9.91% CIS 4.13% Normal urothelium 28.09% Dysplasia / Hyperplasia / CIS / SM* T1: 4 / 2 / - / 4 T2-T4: 45 / 19 / 5 / 8 G1: 2 / - / - / 1	n/a	

<table>
<tr><th>Study</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>G2</td><td>20</td><td>9</td><td>2</td><td>8</td></tr>
<tr><td>G3</td><td>8</td><td>3</td><td>-</td><td>2</td></tr>
<tr><td>G4</td><td>19</td><td>9</td><td>3</td><td>1</td></tr>
</table>
*Squamous metaplasia

All cases of CIS were in the recurrent group</td><td></td><td></td></tr>
<tr><td>Vicente-Rodriguez 1987</td><td>Retrospective cohort study

1981-1985</td><td>N=457 without previous treatment</td><td>
<table>
<tr><td>Male</td><td>409 (89%)</td></tr>
<tr><td>Female</td><td>48 (11%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Mean age</td><td>63 yrs</td></tr>
<tr><td>Age range</td><td>18-89</td></tr>
<tr><td></td><td></td></tr>
<tr><td>G1</td><td>76 (17%)</td></tr>
<tr><td>G2</td><td>225 (49%)</td></tr>
<tr><td>G3</td><td>152 (33%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Ta-T1</td><td>314 (69%)</td></tr>
<tr><td>T2-T3</td><td>109 (24%)</td></tr>
<tr><td>Tx</td><td>30 (7%)</td></tr>
</table>
</td><td>TURBT up to deep muscle layer and R biopsies performed on all patients with flexible forceps in the trigone, behind the trigone, on the right and left lateral walls and vesical dome.
2,272 biopsies performed in 457 patients.
109 were MIBC and in 53 of these radical cystectomy was performed.</td><td>n/a</td><td>n/a</td><td>
<table>
<tr><td></td><td>CIS on Rbx</td></tr>
<tr><td>G1 (76)</td><td>4 (5%)</td></tr>
<tr><td>G2 (225)</td><td>33 (14.66%)</td></tr>
<tr><td>G3(152)</td><td>58 (38.16%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Ta-T1 (314)</td><td>52 (16.56%)</td></tr>
<tr><td>T2-T3 (109)</td><td>42 (38.63%)</td></tr>
<tr><td>Tx (30)</td><td>2 (6.66%)</td></tr>
</table>
</td><td>n/a</td><td></td></tr>
<tr><td>Van der Meijden 1999</td><td>Data from 2 RCTs of intravesical therapy after TUR</td><td>N=512 patients (EORTC 30863)

N=957 (EORTC 30911)</td><td>EORTC 30863 - patients with solitary Ta, T1 tumours (primary or recurrent). 78% M / 22% F
Low risk for recurrence and progression

EORTC 30911 – patients with intermediate and high risk (multiple or recurrent) Ta, T1 tumours. 80% M / 20% F.</td><td>EORTC 30863 – R biopsies taken from normal-appearing urothelium with cold cup forceps in 393 patients.

EORTC 30911 – Multiple R cold cup biopsies taken from preselected sites in normal-appearing urothelium: prostatic urethra, ureteral orifices, right wall, left wall, anterior wall, posterior wall, dome and bladder neck in 602 patients.</td><td>n/a</td><td>n/a</td><td>EORTC 30863 – No abnormalities found in 376/393 (95.6%) of patients

<table>
<tr><td></td><td>CIS</td><td>Ta</td><td>≥T1</td><td>other</td></tr>
<tr><td>Ta</td><td>2</td><td>1</td><td>0</td><td>8</td></tr>
<tr><td>T1</td><td>4</td><td>1</td><td>0</td><td>1</td></tr>
<tr><td>Total</td><td>6
1.5%</td><td>2
0.5 %</td><td>0</td><td>9
2.3%</td></tr>
</table>

EORTC 30911 – No malignancy found in R biopsies of 532/602 (88.4%) of patients.

<table>
<tr><td></td><td>Ta</td><td>T1</td><td>>T1</td><td>CIS*</td></tr>
<tr><td>T0 (28)</td><td>6</td><td>0</td><td>0</td><td></td></tr>
<tr><td>Ta (368)</td><td>32</td><td>3</td><td>0</td><td></td></tr>
</table>
</td><td>Not reported</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>T1 (206)</td><td>14</td><td>14</td><td>1</td><td></td></tr>
<tr><td>Total (602)</td><td>52 8.6%</td><td>17 2.8%</td><td>1 0.2%</td><td>21 3.5%</td></tr>
</table>
* At least 21 patients had CIS in random biopsy – only 29 patients had information available on CIS in R biopsy
</td><td></td><td></td></tr>
<tr><td>Witjes 1992</td><td>Prospective cohort study

1983-1990</td><td>N=1026 superficial TCC of bladder</td><td>842 (82%) Male (mean age65.8±11.2 years)
184 (18%) Female (mean age 65.6 ±12.9 years)
<table>
<tr><td>Ta</td><td>691 (67%)</td></tr>
<tr><td>T1</td><td>335 (33%)</td></tr>
<tr><td>G1</td><td>370 (36%)</td></tr>
<tr><td>G2</td><td>469 (46%)</td></tr>
<tr><td>G3</td><td>197 (19%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>solitary</td><td>741 (72%)</td></tr>
<tr><td>multiple</td><td>281 (27%)</td></tr>
</table>
</td><td>TUR performed as initial therapy plus 4 random biopsies from left and right lateral wall, dome and trigone of normal looking mucosa with cold cup technique during initial TUR</td><td>n/a</td><td>Mean 3.4 years</td><td>Patients with abnormal R biopsy (dysplasia and/or CIS): 217/1026 (21.2%)

2-year risk for recurrence was 44.5% in normal R biopsy group and 47.5% in abnormal R biopsy group.
R biopsy result was not a significant prognostic factor for recurrence in univariate (p=0.14) or multivariate analyses (p=0.31)</td><td>Not reported</td><td></td></tr>
</table>

2.3 Urinary Biomarkers

Review question: What are the diagnostic accuracies of urine testing technologies for new and recurrent bladder cancer?

Rationale

Urine examination for bladder tumours includes conventional cytological examination and the relatively limited use of adjunctive tools such as NMP22, FISH (UroVysion) and ImmunoCyt. Although other urine tests are in development, none are yet routinely available and there is insufficient evidence to consider them at this time.

The need for higher sensitivity in detection of tumours (new and recurrent) has driven the search for a test that would either supplement or replace urine cytology. The topic is contentious because urine cytology, despite the above limitations, is relatively cheap and easily accessible while the use of markers is associated with additional cost and expertise in interpretation and of uncertain benefit, particularly if used without cytology.

The value of using markers in defined clinical settings e.g. investigation of haematuria (new cases) and follow up of patients under surveillance for bladder tumours (recurrent cases) would be a valuable recommendation if supported by available evidence.

Question in PICO format

Population	Index tests	Reference standard tests	Outcomes
Patients with suspected bladder cancer (new or recurrent)	Urinary cytology Nuclear matrix protein (NMP22) FISH (UroVysion) ImmunoCyt	Cystoscopy & biopsy	• Diagnostic yield • Sensitivity • Specificity

METHODS

Information sources

A relevant Health Technology Assessment (HTA) was published in 2010 (Mowatt *et al.*, 2010), which reviewed the diagnostic accuracy of urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology. The literature search was updated for this evidence review.

Selection of studies

The same exclusion and inclusion criteria used in the HTA were used to guide the literature search. To be included, studies reporting test performance had to report the absolute numbers of true positives, false positives, false negatives and true negatives, or provide information allowing their calculation. The reference standard was histopathological examination of biopsied tissue. Studies with fewer than 100 participants were excluded. Studies reported as abstracts only were excluded.

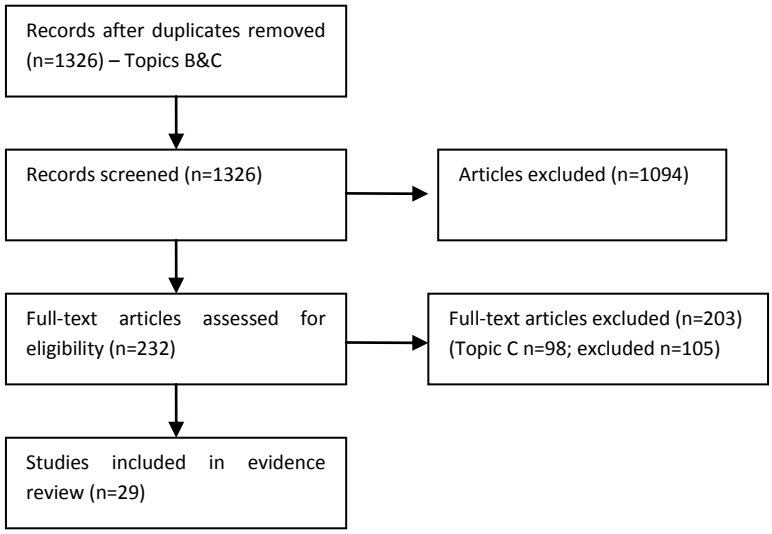
Data synthesis

There were no new studies reporting the test performance of ImmunoCyt. Nine studies were identified relating to NMP22, nine relating to FISH and 21 reporting the test performance of cytology. Where possible these studies were added to the data from the HTA and pooled analysis was conducted using the bivariate model in accordance with the recommendations of the Cochrane Collaboration. For patient-level analysis, pooled estimates with 95% CIs for sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios (DORs) were presented. For specimen and stage/grade level of analysis the median (range) sensitivity and specificity across studies were presented. If the number of specimens reported by a study was one per patient included in the analysis then this was considered as a patient-level analysis. Studies reporting patient- and specimen-level analysis for CIS were included in the section on stage/grade analysis. In the HTA, test performance was presented in terms of the detection of stage and grade of non-muscle-invasive bladder cancer in two broad categories: (1) less aggressive, lower risk tumours (pTa, G1, G2) and (2) more aggressive, higher risk tumours (pT1, G3, CIS). For this evidence review, the median (range) sensitivity across studies for invasive bladder cancer (≥pT2) has also been calculated.

RESULTS

Result of the literature searches

Figure 13. Study flow diagram



Study quality and results

The methodological quality of the biomarker and cytology studies was assessed using a modified version of the QUADAS tool containing 14 questions. The results of the QUADAS quality assessment for the urinary tests are shown in Figures 14-17.

Figure 14. Summary of quality assessment of ImmunoCyt studies (% of studies)

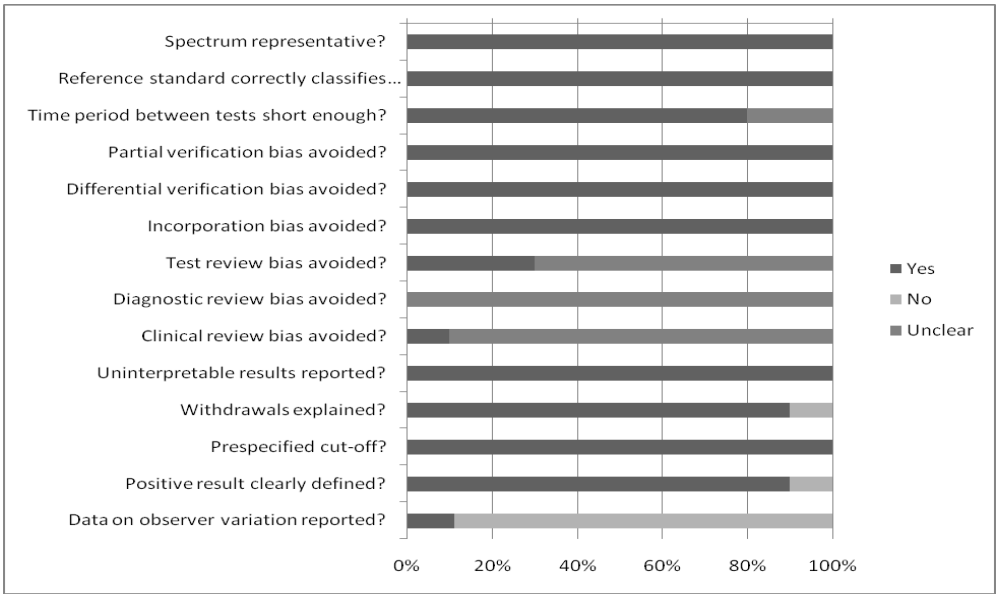


Figure 15. Summary of quality assessment of FISH studies (% of studies)

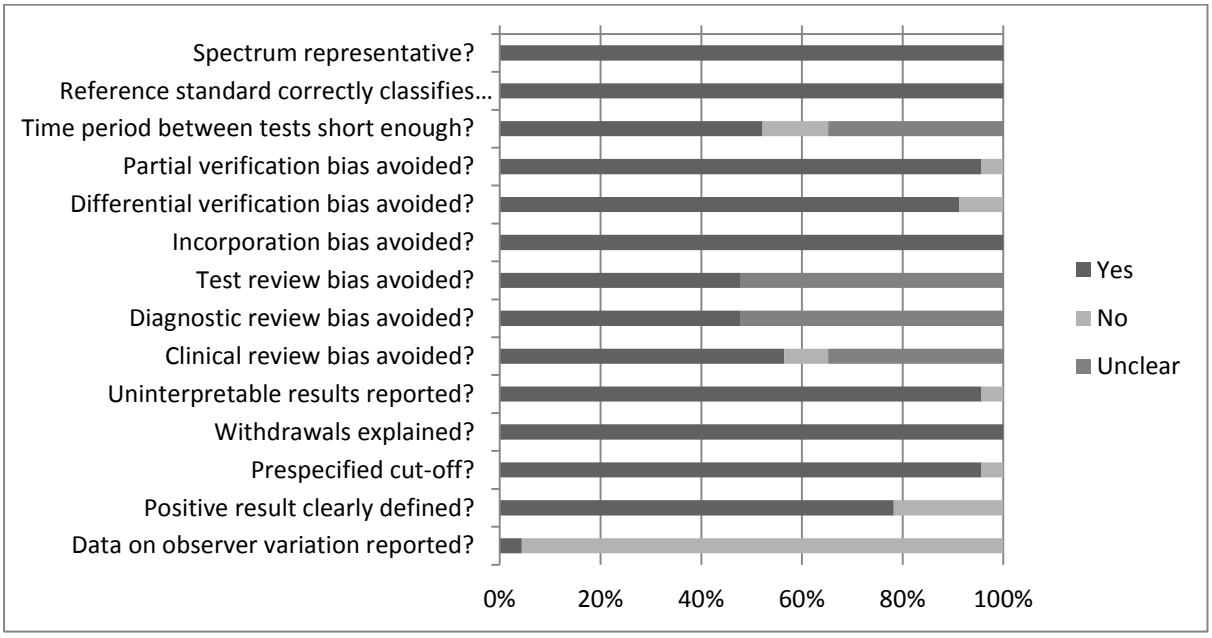


Figure 16. Summary of quality assessment of NMP22 studies (% of studies)

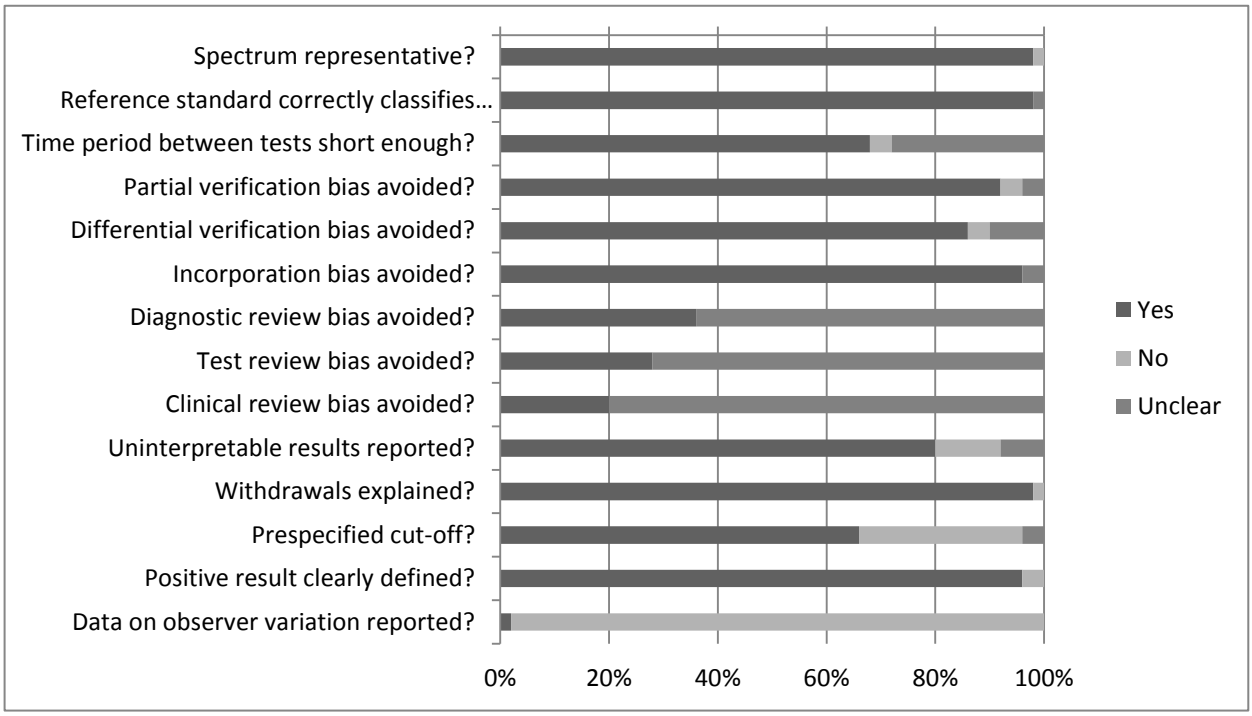
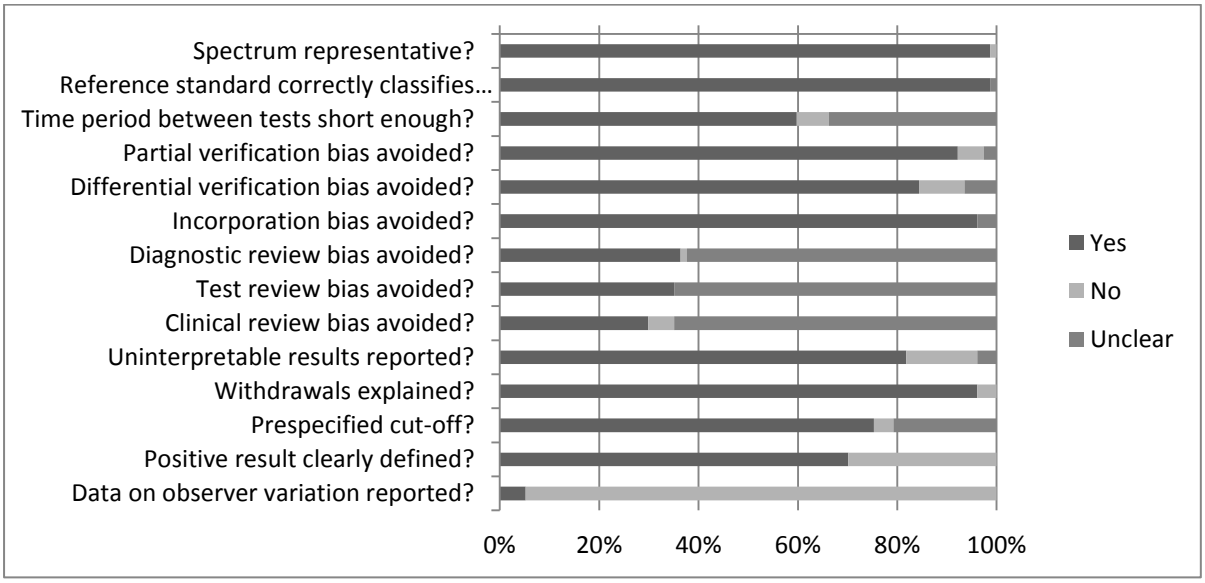


Figure 17. Summary of quality assessment of cytology studies (% of studies)



Evidence statements

A total of 100 studies, reporting the test performance of biomarkers (FISH, ImmunoCyt, and NMP22) and cytology in detecting bladder cancer were included in this evidence review. In total, 23 studies enrolling 5735 participants reported on FISH, 10 studies enrolling 4199 participants reported on ImmunoCyt, 50 studies enrolling 19,190 participants reported on NMP22 and 77 studies enrolling 35,125 participants reported on cytology. Pooled estimates with 95% CIs for sensitivity, specificity,

positive and negative likelihood ratios and DORs for each of the tests were undertaken for patient-level analysis. Table 19 shows the pooled estimates for sensitivity, specificity and DOR for each of the tests. Sensitivity was highest for ImmunoCyt at 84% (95% CI 77% to 91%) and lowest for cytology at 46% (95% CI 40% to 52%). ImmunoCyt (84%, 95% CI 77% to 91%) had higher sensitivity than NMP22 (68%, 95% CI 63% to 73%), with the lack of overlap of the CIs supporting evidence of a difference in sensitivity between the tests in favour of ImmunoCyt. FISH (72%, 95% CI 62% to 80%), ImmunoCyt (84%, 95% CI 77% to 91%) and NMP22 (68%, 95% CI 63% to 73%) all had higher sensitivity than cytology (46%, 95% CI 40% to 52%), and again the lack of overlap between the biomarker and cytology CIs supporting evidence of a difference in sensitivity in favour of the biomarkers over cytology. Although sensitivity was highest for ImmunoCyt and lowest for cytology, this situation was reversed for specificity, which was highest for cytology at 95% (95% CI 93% to 96%) and lowest for ImmunoCyt at 75% (95% CI 68% to 83%). Cytology (95%, 95% CI 93% to 96%) had higher specificity than FISH (86%, 95% CI 79% to 90%), ImmunoCyt (75%, 95% CI 68% to 83%) or NMP22 (80%, 95% CI 75% to 84%), with the lack of overlap between the cytology and biomarker CIs supporting evidence of a difference in specificity in favour of cytology over the biomarkers.

Diagnostic odds ratio (DORs) (95% CI) ranged from 9 (6 to 12) to 16 (12 to 23), with higher DORs indicating a better ability of the test to differentiate between those with bladder cancer and those without. Based on the DOR values, ImmunoCyt, FISH and cytology performed similarly well [16 (6 to 26), 15 (9 to 27), and 16 (12 to 23), respectively], and NMP22 relatively poorly [9 (6 to 12)]. However, it should be noted that the DOR CIs for each of the tests are fairly wide and all overlap, which limits any firm conclusions that can be drawn from these results. Across studies the median (range) PPV was highest for FISH at 71% (27% to 99%) and cytology at 70% (0% to 100%), followed by ImmunoCyt at 54% (26% to 70%) and NMP22 at 48% (8% to 94%). The median (range) NPV was highest for ImmunoCyt at 93% (86% to 100%), followed by FISH at 87% (36% to 97%), NMP22 at 86% (44% to 100%) and cytology at 83% (27% to 100%). However, predictive values are affected by disease prevalence, which is rarely constant across studies, and therefore these data should be interpreted with caution. There was also heterogeneity across the studies included in the pooled estimates, especially for cytology and FISH. This may be due to the variation in participants across studies (including both those with and without a history of bladder cancer), and the interpretation of the test by the clinician (especially for cytology).

Table 20 summarises the sensitivity of the tests in detecting stage/grade of tumour. ImmunoCyt had the highest median sensitivity across studies (81%) for detection of less aggressive/lower risk tumours whereas FISH had the highest median sensitivity across studies (95%) for detection of more aggressive/higher risk tumours and invasive tumours (90%). For detection of CIS the median sensitivity across studies for both UroVysion FISH and ImmunoCyt was 100%. Cytology had the lowest sensitivity across studies for detecting less aggressive/lower risk tumours (27%), more aggressive/higher risk tumours (69%), invasive tumours (78%) and also CIS (78%). The median sensitivity across studies for each test was consistently higher for the detection of more aggressive/higher risk tumours than it was for the detection of less aggressive, lower risk tumours. The range of sensitivities across studies for all of the tests was very wide and therefore some caution is warranted when interpreting these results.

Table 19. Summary of pooled estimate results for biomarkers and cytology for patient-based detection of bladder cancer

Test	No. of studies	No. analysed	Common cut-off	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)
FISH	18	3,766	Gain of more than one or more than two chromosomes	72 (62 to 80)	86 (79 to 90)	15 (9 to 27)
ImmunoCyt	8	2,896	At least one green or one red fluorescent cell	84 (77 to 91)	75 (68 to 83)	16 (6 to 26)
NMP22	37	15,237	≥10 U/ml	68 (63 to 73)	80 (75 to 84)	9 (6 to 12)
Cytology	52	24,183	Cytologist subjective judgement	46 (40 to 52)	95 (93 to 96)	16 (12 to 23)

Table 20. Summary of median (range) sensitivity of tests across studies for patient-level detection of stage/grade of bladder cancer

Test	No. of studies (patients)[a]	Lower risk, median (range) sensitivity	No. of studies (patients)[a]	Higher risk including CIS, median (range) sensitivity	No. of studies (patients)[a]	CIS, median (range) sensitivity	No. of studies (patients)[a]	Invasive, median (range) sensitivity
FISH	10 (2164)	65 (32 to 100)	10 (2164)	95 (50 to 100)	8 (1067)	100 (50 to 100)	6 (1153)	90 (67 to 100)
Immuno Cyt	6 (2502)	81 (55 to 90)	6 (2502)	90 (67 to 100)	6 (2502)	100 (67 to 100)	6 (2502)	87 (67 to 100)
NMP22	22 (7195)	52 (0 to 94)	22 (8996)	79 (0 to 100)	13 (4618)	80 (0 to 100)	20 (9569)	86 (33 to 100)
Cytology	32 (14,069)	28 (0 to 93)	32 (14,069)	71 (0 to 100)	18 (7014)	76 (0 to 100)	29 (13,222)	78 (0 to 100)
a The number of patients refers to the number included in the overall analysis by the studies								

References to included studies

Ahn, JS et al. The clinical usefulness of nuclear matrix protein-22 in patients with atypical urine cytology. Korean Journal of Urology 2011; 52(9): 603-606.

Ajit, D, Dighe, S, and Desai, S. Has urine cytology a role to play in the era of fluorescence in situ hybridization? Acta Cytologica 2010; 54(6): 1118-1122.

Blick, CG et al. Evaluation of diagnostic strategies for bladder cancer using computed tomography (CT) urography, flexible cystoscopy and voided urine cytology: results for 778 patients from a hospital haematuria clinic. BJU International 2012; 110(1): 84-94.

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Evidence tables

Study	Participants	Tests	Outcomes summary
Bott 2008 Study design: C-SD Time period: Apr 2005 to Dec 2007 Country: UK	Enrolled:590; analysed: 590 No previous history of BC: NS; history of BC: NS Age (years): mean 65 (S.D. 14.3) Sex: 369 M, 221 F	Tests and cut-off used: NMP22 (point of care), cut off NS	Unit of analysis: patient (n=590) Sensitivity: 56% Specificity: 94%
Gudjonsson 2008 Study design: C-SD Time period: Oct 2004 to Nov 2005 Country: Sweden	Enrolled: 158 ; analysed: 158 No previous history of BC: 0; history of BC: 158 Age (years): NS Sex: NS	Tests and cut-off used: FISH, minimum of four cells with gains of two or more chromosomes or 12 or more cells with homozygous loss of the 9p21 locus; cytology (VU) suspicious classed as positive	Unit of analysis: Patient Sensitivity: 30% (FISH) 22% (cytology) Specificity: 95% (FISH) 98% (cytology)
Viswanath 2008 Study design: CC-SD Time period: Jun 2003 to Nov 2004 Country: UK	Enrolled: 1000; analysed: 986 No previous history of BC: NS; history of BC: NS Age (years): NS Sex: NS	Tests and cut-off used: Cytology, all abnormal cells classed as positive	Unit of analysis: Patient Sensitivity: 59% Specificity: 94%
Brimo 2009 Study design: C-SD Time period: Jan 2006 to Jun	Enrolled: 282; analysed: 282 No previous history of BC: NS; history of BC: NS	Tests and cut-off used: Cytology, all atypical cells considered negative	Unit of analysis: Specimen Sensitivity: 28% Specificity: 86%

Study	Participants	Tests	Outcomes summary
2008 Country: USA	Age (years): NS Sex: NS		
Ferra 2009 Study design: C-SD Time period: NS Country: USA	Enrolled:140; analysed: NS No previous history of BC:NS; history of BC: NS Age (years): mean 69 (26-92) Sex: NS	Tests and cut-off used: FISH (UroVysion), multiple chromosomal gains (>2) of chromosomes 3, 7, or 17 in at least 4 cells or homozygous loss of 9p21 in at least 12 cells	Unit of analysis: Specimen Sensitivity: 68% Specificity: 40%
Gupta 2009 Study design: C-SD Time period: Feb 2004 to Aug 2005 Country: India	Enrolled: 145; analysed: 145 No previous history of BC: 0; history of BC: 145 Age (years): mean 57 (25-83) Sex: NS	Tests and cut-off used: NMP22 BladderChek; Cytology (VU) inconclusive classified as negative	Unit of analysis: Patient Sensitivity: 86% (NMP22) 39% (Cytology) 93% (MNP22+cytology) Specificity: 78% (NMP22) 97% (Cytology) 75% (NMP22+cytology)
Hara 2009 Study design: C-SD Time period: Jan 1992 to Aug 2006 Country: Japan	Enrolled: 127; analysed: 127 No previous history of BC:0; history of BC: 127 Age (years): median 71 (45-87) Sex: 107 M, 20 F	Tests and cut-off used: Cytology, suspicious classed as negative	Unit of analysis: Patient Sensitivity: 41% Specificity: 84%
Kwak 2009 Study design: C-SD Time period: Apr 2006 to Jul 2007 Country: Korea	Enrolled: 308; analysed: 308 No previous history of BC: 247; history of BC: 61 Age (years): mean 60 (±12) Sex: 205 M, 103 F	Tests and cut-off used: FISH multiple chromosomal gains (>2) of chromosomes 3, 7, or 17 in at least 4 cells or homozygous loss of 9p21 in at least 12 cells; Cytology, suggestive of malignancy and positive pooled together	Unit of analysis: Patient Sensitivity: 56% (FISH), 27% (Cytology) Specificity: 90% (FISH), 63% (Cytology)
Turner 2010 Study design: C-SD Time period: Oct 2007 to)ct 2008 Country: UK	Enrolled: 219; analysed: 219 No previous history of BC: NS; history of BC: NS Age (years): NS Sex: NS	Tests and cut-off used: NMP22 (BladderChek)	Unit of analysis: Patient Sensitivity: 70% Specificity: 93%
Choi 2010 Study design: C-SD Time period: Feb 2006 to Sep 2009 Country: Korea	Enrolled:1070; analysed: 1070 No previous history of BC:808; history of BC: 262 Age (years): mean 59 Sex: 650 M, 420 F	Tests and cut-off used: NMP22 BladderChek; Cytology (NS)	Unit of analysis: Patient Sensitivity: 78% (NMP22); 46% (Cytology) Specificity: 89% (NMP22); 98% (Cytology)
Feifer 2010 Study design: CC-SD Time period: Jul 2005 to Jan 2008 Country: Canada	Enrolled: 200; analysed: 200 No previous history of BC: O; history of BC: 200 Age (years): median 64 (44-80) Sex: 132 M, 68 F	Tests and cut-off used: Cytology, atypical considered positive	Unit of analysis: Patient Sensitivity: 50% Specificity: 90%
Munro 2012 Study design: CC-SD Time period: 2005 Country: UK	Enrolled: 503; analysed: 478 No previous history of BC:NS; history of BC: NS Age (years): median 67 (17-100) Sex: 371 M, 132 F	Tests and cut-off used: Cytology, atypical classed as positive	Unit of analysis: Patient Sensitivity: 66% Specificity: 90%
Ahn 2011 Study design: CC-SD Time period: Jan 2004 to Dec 2009 Country: Korea	Enrolled: 275; analysed: 275 No previous history of BC: 143; history of BC: 132 Age (years): NS Sex: NS	Tests and cut-off used: NMP22 BladderChek (patients with atypical cytology)	Unit of analysis: Patient Sensitivity: 68% Specificity: 80%
Bravaccini 2011 Study design: CC-SD	Enrolled:289; analysed:289 No previous history of BC:NS;	Tests and cut-off used: Cytology (NS)	Unit of analysis: Patient Sensitivity: 39%

Study	Participants	Tests	Outcomes summary
Time period: Jan 2007 to Jun 2008 Country: Italy	history of BC: NS Age (years): median 70 (28-92) Sex: 238 M, 51 F		Specificity: 83%
Ajit 2009 Study design: C-SD Time period: 2000 to 2004 Country: India	Enrolled:951; analysed: 652 No previous history of BC:652; history of BC: 0 Age (years): mean 54 Sex: NS	Tests and cut-off used: Cytology (VU)	Unit of analysis: Patient Sensitivity: 69% Specificity: 91%
Galvan 2011 Study design: CC-SD Time period: Nov 2007 to Nov 2008 Country: Spain	Enrolled:223; analysed: ns No previous history of BC:0; history of BC: 223 Age (years): median 73 (31-91) Sex:182 M, 41 F	Tests and cut-off used: FISH (UroVysion) ≥5 cells with polysomy or >10 nuclei gaining a single chromosome or the presence of >50% of nuclei, with losses of 1 or both 9p21 signals; Cytology (VU); White light cystoscopy	Unit of analysis: Specimen Sensitivity: 93% (FISH); 14% (Cytology); 82% (Cystoscopy); 100% (FISH+cystoscopy) Specificity: 92% (FISH); 100% (Cytology); 90% (Cystoscopy); 85% (FISH + cystoscopy)
Hwang 2011 Study design: C-SD Time period: Apr 2008 to June 2009 Country: Korea	Enrolled:1021; analysed: 1021 No previous history of BC: 424; history of BC: 597 Age (years): mean 65 Sex: 776 M, 245 F	Tests and cut-off used: NMP22 BladderChek (10 U/ml); Cytology (BW), outright positive considered positive	Unit of analysis: Patient Sensitivity: 32% (NMP22); 38% (Cytology); 53% (NMP22 + cytology) Specificity: 97% (NMP22); 98% (Cytology); 95% (NMP22 + cytology)
Blick 2011 Study design: CC-SD Time period: Mar 2004 to Dec 2007 Country: UK	Enrolled:778; analysed: 778 No previous history of BC:778; history of BC: 0 Age (years): mean 67 (37-97) Sex: 619 M, 159 F	Tests and cut-off used: Cytology (VU), suspicious atypia and malignant classed as positive	Unit of analysis: Patient Sensitivity: 38% Specificity: 98%
Hosseini 2012 Study design: C-SD Time period: Jul 2007 to Feb 2009 Country: Iran	Enrolled:144; analysed: 144 No previous history of BC:0; history of BC: 144 Age (years): mean 62 (26-86) Sex: 125 M, 19 F	Tests and cut-off used: NMP22 (BladderChek); Cytology (VU)	Unit of analysis: Patient Sensitivity: 44% (Cytology); 79% (NMP22) Specificity: 84% (Cytology); 70% (NMP22)
Siddappa 2012 Study design: C-SD Time period: Sep 2007 to Aug 2010 Country: India	Enrolled:1428; analysed:1428 No previous history of BC:NS; history of BC: NS Age (years): mean 46 (6-80) Sex: 1069 M, 359 F	Tests and cut-off used: Cytology (VU), atypical classed as positive	Unit of analysis: Patient Sensitivity: 99% Specificity: 75%
Youssef 2012 Study design: C-SD Time period: Jun 2007 to Jan 2009 Country: USA	Enrolled:142; analysed: 123 No previous history of BC:0; history of BC: 123 Age (years): mean 69 (35-94) Sex: 91 M,32 F	Tests and cut-off used: FISH, ≥4 cells had a gain of ≥2 chromosomes 3,7,17 or when ≥12 cells had loss of two copies of 9p21	Unit of analysis: Patient (with negative cytology) Sensitivity: 24% Specificity: 94%
Sagnak 2011 Study design: C-SD Time period: Oct 2005 to Sep 2007 Country: Turkey	Enrolled:164; analysed: 164 No previous history of BC: 165; history of BC: 0 Age (years): mean 31 (SD, 6.4) Sex: 57 M, 107 F	Tests and cut-off used: NMP22 BladderChek; Cytology (VU)	Unit of analysis: Patient Sensitivity: 100% (NMP22); 0% (Cytology) Specificity: 85% (NMP22); 97% Cytology
Maffezzini 2008 Study design: CC-SD Time period: May 2003 to Dec 2004 Country: Italy	Enrolled:150; analysed: 133 No previous history of BC:0; history of BC: 133 Age (years): mean 68 Sex: 127 M, 23 F	Tests and cut-off used: FISH (UroVysion) ≥4 cells had a gain of ≥2 chromosomes or ≥10 cells with a gain of single chromosome, or ≥10 cells had homozygous loss of 9p21; Cytology (VU)	Unit of analysis: Patient Sensitivity: 75% (FISH); 47% (Cytology) Specificity: 45% (FISH); 69% (Cytology)
Schlomer 2010 Study design: C-SD	Enrolled:216; analysed:186 No previous history of	Tests and cut-off used: FISH, ≥4 cells had a gain of	Unit of analysis: Patient Sensitivity: 80% (History of BC);

Study	Participants	Tests	Outcomes summary
Time period: Jun 2007 to Jan 2009 Country: USA	BC:108; history of BC: 108 Age (years): mean 66 (30-96) Sex: 175 M, F 41	≥2 chromosomes 3,7,17 or when ≥12 cells had loss of two copies of 9p21	67% (No history of BC) Specificity: 67% (History of BC); 93% (No history of BC)
Lotan 2008 Study design: C-SD Time period: May 2006 to June 2007 Country: USA	Enrolled:120; analysed: 116 No previous history of BC: 50; history of BC: 70 Age (years): median 65 (SD 14.4) Sex: 91 M, 29 F	Tests and cut-off used: FISH, ≥4 cells had a gain of ≥2 chromosomes 3,7,17 or when ≥12 cells had loss of two copies of 9p21	Unit of analysis: Sensitivity: 96% (History of BC); 82% (No history of BC) Specificity: 84% (History of BC); 94% (No history of BC)
Kelly 2012 Study design: CC-SD Time period: NS Country: UK	Enrolled: NS; analysed: 1677 No previous history of BC:1677; history of BC: 0 Age (years): mean 61 (SD, 16) Sex: 1040 M, 637 F	Tests and cut-off used: NMP22 (Matritech), 10 U/ml	Unit of analysis: Patient Sensitivity: 53% Specificity: 84%
Mishriki 2013 Study design:C-SD Time period:1999-2007 Country: UK	Enrolled: NS; analysed: 2778 No previous history of BC:NR; history of BC: NR Age: NR Sex:1867 M, 911 F	Tests and cut-off used: Cytology (VU), suspicious classed as positive	Unit of analysis: Patient Sensitivity: 45.4% Specificity: 89.5%
Dimashkieh 2013 Study design: C-SD Time period: 2003-2006 Country: USA	Enrolled: 2870 (specimens); analysed: 1835 (specimens), 957 patients No previous history BC: 652; history of BC: 305 Age: NR Sex: 610 M, 347 F	Tests and cut-off used: Cytology (VU and BW) atypical classed as positive. FISH ≥4 cells had a gain of ≥2 chromosomes 3,7,17 or when ≥12 cells had loss of two copies of 9p21	Unit of analysis: Specimen Sensitivity:62% (FISH); 61% (cytology) Specificity: 90% (FISH); 84% (cytology)
Yafi 2014 Study design: C-SD Time period: 2006 Country: Canada	Enrolled: 1114; analysed; 189 No previous history BC: 28%; history of BC: 61% Age: median 73 years Sex: 910 M, 204 F	Tests and cut-off used: Cytology (VU): atypical classed as negative	Unit of analysis: Specimen Sensitivity: 32% Specificity: 88%

BW, bladder wash; C-SD, cross-sectional diagnostic study; CC-SD, consecutive cross-sectional diagnostic study; NS, not stated; VU, voided urine.

Health Economic Evidence: What are the most effective endoscopic techniques and urine testing technologies for diagnosing new and recurrent bladder cancer?

Review questions

What are the diagnostic accuracies of urine testing technologies for new and recurrent bladder cancer?

Table21: Pico Table For Urine Testing Technologies For New And Recurrent Bladder Cancer

Population	Index tests	Reference standard tests	Outcomes
Patients with suspected bladder cancer (new or recurrent)	• Urinary cytology • Nuclear matrix protein (NMP22) • FISH (UroVysion) • ImmunoCyt	Cystoscopy & biopsy	• Diagnostic yield • Sensitivity • Specificity

What are the most effective endoscopic techniques for diagnosing bladder cancer (for example white light, blue light, narrow band cystoscopy)?

Table 22: Pico Table For Endoscopic Techniques For Diagnosing Bladder Cancer

Population	Index tests	Reference standard	Outcomes
Patients with suspected bladder cancer (new or recurrent)	• White light cystoscopy • Narrow band cystoscopy • Blue light cystoscopy/ Photodynamic diagnosis (PDD) Alone or in combination	Histopathological examination of biopsied tissue	• Diagnostic yield • Sensitivity • Specificity • Process-related morbidity • Health-related quality of life

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country

- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO
- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

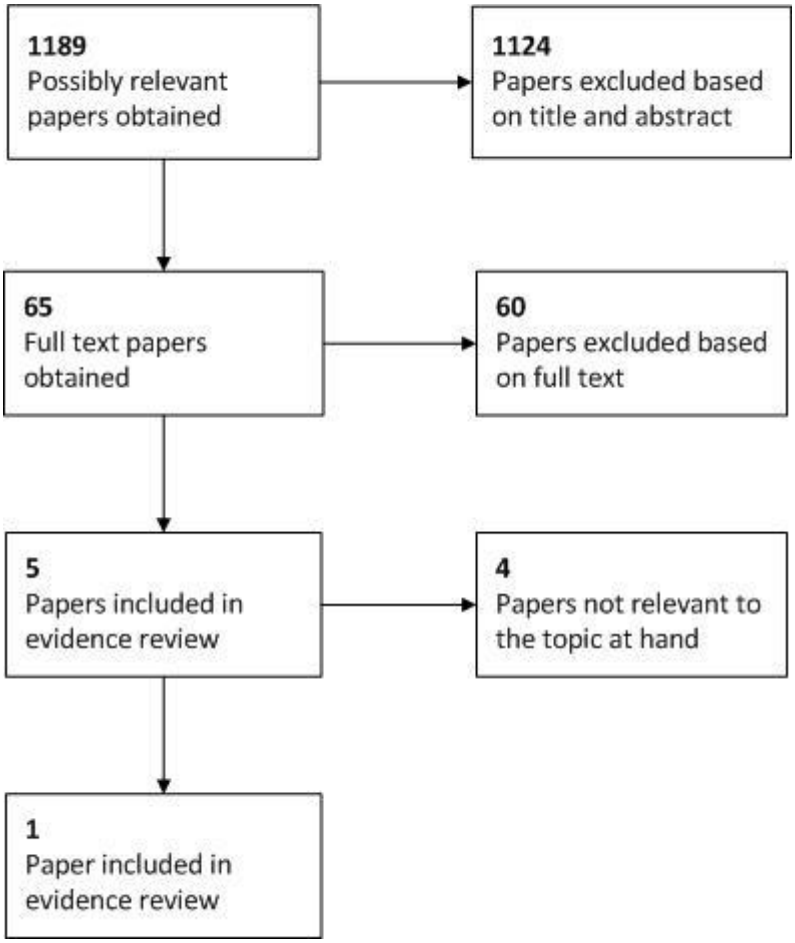
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

Three searches for economic evidence were run over the development of the guideline; one at the start of the process, an update midway through and a further update at the end of the process. The diagram below shows the combined results of the three searches and illustrates the sifting process.

Figure 18: Summary Of Evidence Search And Sifting Process For This Topic



It can be seen that, in total, 1,189 possibly relevant papers were identified. Of these, 1,124 papers were excluded at the initial sifting stage based on the title and abstract while 65 full papers were obtained for appraisal. A further 56 papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, nine papers were included in the systematic review of the economic evidence for this guideline.

One of these nine papers related to the topic at hand and was thus included in the review of published economic evidence for this topic; Mowatt et al. 2010. Mowatt et al. 2010 was a comprehensive report conducted as part of the NIHR HTA programme. The study included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

Quality and applicability of the included study

In most respects, Mowatt et al. 2010 is directly applicable to the decision problem that we are evaluating since it considers relevant comparators in the UK healthcare system. However, the majority of the analyses used life years and not QALYs as the measure of effectiveness. This limits applicability somewhat because QALYs are the effectiveness measure preferred by NICE. No serious limitations were identified with the analysis, which was generally of a very high standard. However

some minor limitations were identified, including the use of expert clinical opinion to estimate some model parameters (in the absence of appropriate data).

Table 23: Table Showing Methodological Quality And Applicability Of The Included Study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		Mowatt et al. 2010
Potentially serious limitations		
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Mowatt et al. 2010 are summarised in the modified GRADE table below.

Table 24: modified grade table showing the included evidence (mowatt et al. 2010) comparing urine tests and endoscopic techniques in the diagnosis of new and recurrent bladder cancer

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Mowatt et al. 2010 NIHR HTA	Men with suspected bladder cancer.	**Full results of base case analysis (using life years [LYs] as effectiveness measure)**						**One-way sensitivity analyses** Numerous one-way sensitivity analyses were conducted. One of the sensitivity analyses is of particular interest because it involved measuring effectiveness using QALYs (the effectiveness measure preferred by NICE). This was done by applying quality of life measures associated with other urological cancers (results shown in table). Additional one-way sensitivity analyses were conducted on key variables identified by the author (using life years as the effectiveness	Partly applicable. High quality evaluation that considers the UK health system. However, in most analyses, NICE's preferred effectiveness measure (QALYs) is not used.	Minor limitations. Most of the input parameters were informed by systematic review. However, in some instances, assumptions were necessary because of a lack of available evidence.
		1. CTL_WLC (CTL_WLC)	£1,043	11.59 LYs	-					
		2. CTL_PDD (CTL_WLC)	£1,094	11.60 LYs	£51	0.01	£3,423			
		3.FISH_WLC (FISH_WLC)	£1,171	11.62 life years	£77	0.01	£5,575			
		4.FISH_PDD (FISH_WLC)	£1,235	11.64 LYs	£64	0.02	£2,762			
		5.NMP22_WLC (NMP22_WLC)	£1,242	11.61 LYs	£6	-0.03	Dominated			
		6.NMP22_PDD (NMP22_WLC)	£1,321	11.62 LYs	£86	-0.02	Dominated			
		7.IMM_WLC (IMM_WLC)	£1,345	11.63 LYs	£109	-0.01	Dominated			
		8. IMM_PDD (IMM_WLC)	£1,458	11.65 LYs	£223	0.01	£28,864			
		9.CSC_CTL_WLC (CTL_WLC)	£1,662	11.62 LYs	£204	-0.03	Dominated			
		10.CSC_FISH_WLC (FISH_WLC)	£1,807	11.63 LYs	£349	-0.02	Dominated			
		11.CSC_NMP22_WLC (NMP22_WLC)	£1,851	11.62 LYs	£393	-0.02	Dominated			
		12.CSC_CTL_PDD (CTL_WLC)	£1,859	11.65 LYs	£401	0	Dominated			

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		13.CSC_WLC (CSC_WLC)	£1,920	11.60 LYs	£462	-0.04	Dominated	measure). Throughout the analyses, one of the following strategies was the most cost-effective strategy (assuming a threshold of £30,000 per life year): • CTL_WLC (CTL_WLC) • CTL_PDD (CTL_PDD) • IMM_PDD (IMM_WLC) • FISH_PDD (FISH_WLC) • CSC_FISH_PDD (FISH_WLC) • CSC_PDD (CSC_WLC) • CSC_IMM_PDD (IMM_WLC) **Probabilistic sensitivity analyses** In addition, a probabilistic sensitivity		
		14.CSC_IMM_WLC (IMM_WLC)	£1,941	11.63 LYs	£483	-0.02	Dominated			
		15.CSC_CTL_WLC (CSC_WLC)	£1,997	11.62 LYs	£539	-0.03	Dominated			
		16.CSC_FISH_PDD (FISH_WLC)	£2,005	11.66 LYs	£547	0.01	£60,284			
		17.CSC_FISH_WLC (CSC_WLC)	£2,042	11.63 LYs	£37	-0.03	Dominated			
		18.CSC_NMP22_WLC (CSC_WLC)	£2,070	11.62 LYs	£65	-0.03	Dominated			
		19.CSC_PDD (CSC_WLC)	£2,082	11.63 LYs	£77	-0.03	Dominated			
		20.CSC_NMP22_PDD (NMP22_WLC)	£2,089	11.65 LYs	£84	-0.01	Dominated			
		21.CSC_IMM_WLC (CSC_WLC)	£2,105	11.63 LYs	£100	-0.03	Dominated			
		22.CSC_CTL_PDD (CSC_WLC)	£2,145	11.64 LYs	£140	-0.01	Dominated			
		23.CSC_IMM_PDD (IMM_WLC)	£2,195	11.66 LYs	£190	<0.01	£309,256			
		24.CSC_FISH_PDD (CSC_WLC)	£2,270	11.66 LYs	£75	0	Dominated			
		25.CSC_NMP22_PDD (CSC_WLC)	£2,318	11.65 LYs	£123	-0.01	Dominated			
		26.CSC_IMM_PDD (CSC_WLC)	£2,370	11.65 LYs	£175	<0.01	£237,863			

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		Base case analysis results without dominated and extendedly dominated options (using LYs as effectiveness measure)						analysis (PSA) was conducted for both the base case analysis and the sensitivity analysis where QALYs are used. In both analyses, the PSA results demonstrated considerable uncertainty. Indeed, there was no clear strategy that would be preferred based on the PSA results. However, in the analysis using QALYs, three strategies were found to have around a 20% probability of being cost-effective over much of the thresholds; CTL-WLC (CTL-WLC), FISH-PDD (FISH-WLC) and CSC-FISH-WLC (FISH-WLC).		
		1. CTL_WLC (CTL_WLC)	£1,043	11.59 LYs	-					
		2. CTL_PDD (CTL_WLC)	£1,094	11.60 LYs	£51	0.01	£3,423			
		4.FISH_PDD (FISH_WLC)	£1,235	11.64 LYs	£141	0.04	£3,806			
		8.IMM_PDD (IMM_WLC)	£1,458	11.65 LYs	£223	0.01	£28,864			
		16.CSC_FISH_PDD (FISH_WLC)	£2,005	11.66 LYs	£547	0.01	£60,284			
		26.CSC_IMM_PDD (CSC_WLC)	£2,370	11.65 LYs	£365	<0.01	£270,375			
		Sensitivity analysis using quality adjusted life years [QALYs] as effectiveness measure								
		1. CTL_WLC (CTL_WLC)	£1,043	9.00 QALYs	-					
		2. CTL_PDD (CTL_WLC)	£1,094	9.01 QALYs	£51	0.01	£4,678			
		4.FISH_PDD (FISH_WLC)	£1,235	9.04 QALYs	£141	0.03	£5,051			
		8.IMM_PDD (IMM_WLC)	£1,458	9.04 QALYs	£223	<0.01	Extendedly dominated			
		16.CSC_FISH_PDD (FISH_WLC)	£2,005	9.05 QALYs	£770	0.01	£66,905			
		19.CSC_PDD (CSC_WLC)	£2,082	9.01 QALYs	£77	-0.04	Dominated			

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		23.CSC_IMM_PDD (IMM_WLC)	£2,195	9.05 QALYs	£190	0	Dominated			
		26.CSC_IMM_PDD (CSC_WLC)	£2,370	9.05 QALYs	£365	0	Dominated			
	Comments: The majority of the analyses use life years as the measure of the effectiveness. Quality adjusted life years (QALYs) are the preferred effectiveness measure of NICE.									

Abbreviations and notation:

CSC – flexible cystoscopy, CTL – cytology, WLC – white light cystoscopy, PDD – photodynamic diagnosis, IMM – immunoCyt urinary biomarker, FISH – FISH urinary biomarker, NMP22 – NMP22 urinary biomarker

The strategies consist of investigations used in initial diagnosis and follow-up. The investigations used in follow are denoted in brackets. For example, a strategy of "FISH_PDD (FISH_WLC)" means that "FISH_PDD" is used in initial diagnosis while "FISH_WLC" is used in follow-up.

Each of the strategies used in diagnosis and follow-up consist of a first line test and a second line test. The 1st line test could be one test (CSC, CTL or urinary biomarker) or a combination of tests (will always include CSC and then either biomarker or CTL or both). The 2nd line test will always be either a PDD or WLC. Patients would need to be positive on both tests to be diagnosed. If negative at the 1st line, then the patient would either receive another urine test or cytology (depending on strategy) or they would not be diagnosed (and would then possibly be followed-up).

Note also that in follow-up, the same 1st line test will be used as in initial diagnosis and the 2nd line test will always be WLC

Evidence statements

While the study is of methodologically high quality, there were concerns about the use of life years as the primary effectiveness measure in the majority of analyses. This makes cost-effectiveness difficult to assess as there is no established cost-effectiveness threshold based on life years in the UK.

However, the results do provide some indication of cost-effectiveness in this area. Firstly, it is notable that, in the base case analysis, most strategies were found to be superior in life year terms to the strategy used in current practice (flexible cystoscopy and white light cystoscopy). Secondly, excluding studies that were either dominated or extendedly dominated in the base case analysis, leaves six strategies that are likely to be candidates for the most cost-effective strategy overall:

1. Cytology and white light cystoscopy used in initial diagnosis and follow-up (CTL_WLC [CTL_WLC]).
2. Cytology and photodynamic diagnosis used in initial diagnosis with cytology and white light cystoscopy used in follow-up (CTL_PDD [CTL_WLC]).
3. FISH and photodynamic diagnosis used in initial diagnosis with FISH and white light cystoscopy used in follow-up (FISH_PDD [FISH_WLC]).
4. Immunocyt and photodynamic diagnosis used in initial diagnosis with Immunocyt and white light cystoscopy used in follow-up (IMM_PDD [IMM_WLC]).
5. Flexible cystoscopy, FISH and photodynamic diagnosis used in initial diagnosis with FISH and white light cystoscopy used in follow-up (CSC_FISH_PDD [FISH_WLC]).
6. Flexible cystoscopy, Immunocyt and photodynamic diagnosis used in initial diagnosis with flexible cystoscopy and white light cystoscopy used in follow-up (CSC_IMM_PDD [CSC_WLC]).

While there were concerns about the applicability of the available quality of life (QoL) data that prevented them being used in the base case analysis, they were included in a sensitivity analysis where quality adjusted life years (QALYs) were generated. This analysis used QoL values from other urological cancers.

When considering the sensitivity analysis using QALYs, the strategy of FISH and photodynamic diagnosis used in initial diagnosis with FISH and white light cystoscopy used in follow-up (FISH_PDD [FISH_WLC]) appears to be the most cost-effective at a threshold of £20,000 per QALY. However, there is a lot of uncertainty around this conclusion because of the strong reservations about using the QoL data.

A probabilistic sensitivity analysis (PSA) was conducted for both the base case analysis and the sensitivity analysis where QALYs are used. In both analyses, the PSA results demonstrated considerable uncertainty. Indeed, there was no clear strategy that would be preferred based on the PSA results.

Overall, it is difficult to fully and robustly assess cost-effectiveness in this area. However, it does appear that strategies involving urinary biomarkers, cytology or PDD provide additional benefits compared to current practice and do so at a cost that society might be willing to pay.

References

1. Mowatt, G., et al. "Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer (Structured abstract)." Health Technology Assessment (2010): 1.

Full evidence table

The full details of the study included in the evidence review are presented in the evidence table below.

Table 25: full evidence table showing the included evidence (mowatt et al. 2010) comparing urine tests and endoscopic techniques in the diagnosis of new and recurrent bladder cancer

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Mowatt et al. **Year:** 2010 **Country:** UK	**Type of analysis:** Cost-effectiveness analysis (using life years or cases of true positives in the base case). A cost-utility analysis was conducted as a sensitivity analysis. **Model structure:** Two part model: 1. Decision tree considering diagnostic tests 2. Follow up of patients after diagnosis using a Markov model **Cycle length:** One year although risk groups considered in the care pathway will be followed for different time	**Inclusion criteria:** People suspected of having bladder cancer. **Exclusion criteria:** Not reported **Base case (population):** A bladder cancer prevalence of 5% was assumed in the base case. Types of cancer and prognostic risk groups applied in the base case: • NMIBC – 75% ▪ Low risk – 10% ▪ Intermediate risk – 45% ▪ High risk – 45% • MIBC – 25% ▪ Local muscle invasive – 75%	The interventions included in the analysis were flexible cystoscopy (CSC), cytology (CTL), three types of biomarkers (NMP22, FISH and ImmunoCyt (IMM)), white light cystoscopy (WLC) and Photodynamic diagnosis (PDD). The model considered strategies used in diagnosis and follow-up. Each strategy consists of a first line test and a second line test. The 1st line test could be one test (CSC, CTL or urinary biomarker) or a combination of tests (will always include	**Effectiveness (LYs):** 1. CTL_WLC (CTL_WLC) 2. CTL_PDD (CTL_WLC) 3. FISH_WLC (FISH_WLC) 4. FISH_PDD (FISH_WLC) 5. NMP22_WLC (NMP22_WLC) 6. NMP22_PDD (NMP22_WLC) 7. IMM_WLC (IMM_WLC) 8. IMM_PDD (IMM_WLC) 9. CSC_CTL_WLC (CTL_WLC) 10. CSC_FISH_WLC (FISH_WLC) 11. CSC_NMP22_WLC (NMP22_WLC) 12. CSC_CTL_PDD (CTL_WLC) 13. CSC_WLC (CSC_WLC) 14. CSC_IMM_WLC (IMM_WLC) 15. CSC_CTL_WLC (CSC_WLC) 16. CSC_FISH_PDD (FISH_WLC) 17. CSC_FISH_WLC (CSC_WLC) 18. CSC_NMP22_WLC (CSC_WLC) 19. CSC_PDD (CSC_WLC) 20. CSC_NMP22_PDD (NMP22_WLC) 21. CSC_IMM_WLC (CSC_WLC) 22.CSC_CTL_PDD (CSC_WLC) 23. CSC_IMM_PDD (IMM_WLC) 24. CSC_FISH_PDD (CSC_WLC)	 11.59 11.60 11.62 11.64 11.61 11.62 11.63 11.65 11.62 11.63 11.62 11.65 11.60 11.63 11.62 11.66 11.63 11.62 11.63 11.65 11.63 11.64 11.66 11.66	**Funding:** This report was commissioned by the NIHR HTA Programme **Comments** Authors had no competing interests.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	periods: • Twelve months for low risk • Six months for intermediate risk • Three months for high risk **Time horizon:** 20 year time horizon **Perspective:** Third party payer perspective (NHS) **Source of base-line data:** The bladder cancer prevalence rate applied in the base case was an assumed value of 5%. The authors state that it was not literature based because it varies considerably among subgroups with different symptoms (1-20%). Alternative prevalence	▪ Metastases – 25% **Sample size:** Hypothetical cohort of 1000 patients. **Age:** A baseline age of 67 years old was applied (based on the results of the systematic review). **Gender:** Not explicitly stated but appears to be 70% male and 30% female based on all cause mortality calculations. All cause mortality appears to be the only model parameter that would be affected by gender. **Subgroup analysis:** None.	CSC and then either biomarker or CTL or both). The 2nd line test will always be either a PDD or WLC. Patients would need to be positive on both tests to be diagnosed. If negative at the 1st line, then the patient would either receive another urine test or cytology (depending on strategy) or they would not be diagnosed (and would then possibly be followed-up). The 26 different strategies of initial diagnosis and follow-up considered in the model are shown below. Note that the investigations used in follow are denoted in brackets. Note also	25. CSC_NMP22_PDD (CSC_WLC) 26. CSC_IMM_PDD (CSC_WLC) **Total costs:** 1. CTL_WLC (CTL_WLC) 2. CTL_PDD (CTL_WLC) 3. FISH_WLC (FISH_WLC) 4. FISH_PDD (FISH_WLC) 5. NMP22_WLC (NMP22_WLC) 6. NMP22_PDD (NMP22_WLC) 7. IMM_WLC (IMM_WLC) 8. IMM_PDD (IMM_WLC) 9. CSC_CTL_WLC (CTL_WLC) 10. CSC_FISH_WLC (FISH_WLC) 11. CSC_NMP22_WLC (NMP22_WLC) 12. CSC_CTL_PDD (CTL_WLC) 13. CSC_WLC (CSC_WLC) 14. CSC_IMM_WLC (IMM_WLC) 15. CSC_CTL_WLC (CSC_WLC) 16. CSC_FISH_PDD (FISH_WLC) 17. CSC_FISH_WLC (CSC_WLC) 18. CSC_NMP22_WLC (CSC_WLC) 19. CSC_PDD (CSC_WLC) 20. CSC_NMP22_PDD (NMP22_WLC) 21. CSC_IMM_WLC (CSC_WLC) 22.CSC_CTL_PDD (CSC_WLC) 23. CSC_IMM_PDD (IMM_WLC) 24. CSC_FISH_PDD (CSC_WLC) 25. CSC_NMP22_PDD (CSC_WLC)	11.65 11.65 £1,043 £1,094 £1,171 £1,235 £1,242 £1,321 £1,345 £1,458 £1,662 £1,807 £1,851 £1,859 £1,920 £1,941 £1,997 £2,005 £2,042 £2,070 £2,082 £2,089 £2,105 £2,145 £2,195 £2,270 £2,318	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	rates were explored in the sensitivity analysis. The proportion of patients with muscle invasive and non-muscle invasive bladder cancer (MIBC and NMIBC) were based on the literature reviewed and opinions from clinical experts. The risk subgroups within NMIBC and MIBC were also based on literature reviewed and opinions from clinical experts. Prognostic risk groups in NMIBC were categorised using a combination of the initial classification system from Millán-Rodriguez et al. 2000 and the classifications at three months and follow-up from Parmar et al. 1989. Annual rates of	The authors state that they intended to perform subgroup analysis but did not because of a lack of relevant data.	that in follow-up, the same 1st line test will be used as in initial diagnosis and the 2nd line test is always WLC. 26 Strategies of **initial diagnosis and follow-up:** 1. CTL_WLC (CTL_WLC) 2. CTL_PDD (CTL_WLC) 3. FISH_WLC (FISH_WLC) 4. FISH_PDD (FISH_WLC) 5. NMP22_WLC (NMP22_WLC) 6. NMP22_PDD (NMP22_WLC) 7. IMM_WLC (IMM_WLC) 8. IMM_PDD	26. CSC_IMM_PDD (CSC_WLC) **ICER (cost per LY):** 1. CTL_WLC (CTL_WLC) 2. CTL_PDD (CTL_WLC) 3. FISH_WLC (FISH_WLC) 4. FISH_PDD (FISH_WLC) 5. NMP22_WLC (NMP22_WLC) 6. NMP22_PDD (NMP22_WLC) 7. IMM_WLC (IMM_WLC) 8. IMM_PDD (IMM_WLC) 9. CSC_CTL_WLC (CTL_WLC) 10. CSC_FISH_WLC (FISH_WLC) 11. CSC_NMP22_WLC (NMP22_WLC) 12. CSC_CTL_PDD (CTL_WLC) 13. CSC_WLC (CSC_WLC) 14. CSC_IMM_WLC (IMM_WLC) 15. CSC_CTL_WLC (CSC_WLC) 16. CSC_FISH_PDD (FISH_WLC) 17. CSC_FISH_WLC (CSC_WLC) 18. CSC_NMP22_WLC (CSC_WLC) 19. CSC_PDD (CSC_WLC) 20. CSC_NMP22_PDD (NMP22_WLC) 21. CSC_IMM_WLC (CSC_WLC) 22.CSC_CTL_PDD (CSC_WLC) 23. CSC_IMM_PDD (IMM_WLC) 24. CSC_FISH_PDD (CSC_WLC) 25. CSC_NMP22_PDD (CSC_WLC) 26. CSC_IMM_PDD (CSC_WLC)	£2,370 - £3,423 £5,575 £2,762 Dominated Dominated Dominated £28,864 Dominated Dominated Dominated Dominated Dominated Dominated £60,284 Dominated Dominated Dominated Dominated Dominated £309,256 Dominated Dominated £237,863	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	recurrence, progression and cancer related mortality for patients with NMIBC were sourced from a retrospective cohort study of 1529 patients with primary NMIBC in Spain in 1968-96 (Millán-Rodriguez et al. 2000). For MIBC patients, annual rates of recurrence, progression and mortality caused by local muscle invasive disease were sourced from a Canadian retrospective cohort study of 1,054 MIBC patients undergoing radical cystectomy between 1971 and 1999 (Stein et al. 2001). Probabilities of mortality for metastases were sourced from a Danish RCT investigating the long term survival of patients with metastatic bladder		(IMM_WLC) 9. CSC_CTL_WLC (CTL_WLC) 10. CSC_FISH_WLC (FISH_WLC) 11. CSC_NMP22_WLC (NMP22_WLC) 12. CSC_CTL_PDD (CTL_WLC) 13. CSC_WLC (CSC_WLC) 14. CSC_IMM_WLC (IMM_WLC) 15. CSC_CTL_WLC (CSC_WLC) 16. CSC_FISH_PDD (FISH_WLC) 17. CSC_FISH_WLC (CSC_WLC)	**Results with dominated and extended dominated options removed:** 1. CTL_WLC (CTL_WLC) 2. CTL_PDD (CTL_WLC) 4. FISH_PDD (FISH_WLC) 8. IMM_PDD (IMM_WLC) 16. CSC_FISH_PDD (FISH_WLC) 26. CSC_IMM_PDD (CSC_WLC) The authors suggest that since people will be in less than full health it is likely that the incremental cost per QALY will be greater than £20,000 for all strategies apart from 2, 3 and 4. They further state that the incremental cost per QALY for strategy 8 may be greater than £20,000 but less than £30,000 as long as the average annual QoL score is 0.65. **<u>Uncertainty:</u>** **One-way sensitivity analyses** The authors conducted one-way sensitivity analysis on the variables	- £3,423 £3,806 £28,864 £60,284 £270,375	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	cancer treated with chemotherapy (von der Maase et al. 2005). All cause mortality rates were sourced from published UK life tables for 2004-2006. **<u>Source of effectiveness data:</u>** Data on the sensitivity and specificity of tests were derived from a systematic review of the available clinical evidence, conducted by the authors. For flexible cystoscopy (CSC), there were no data available from the systematic review. Therefore, it was assumed that the accuracy of CSC is equivalent to white light rigid cystoscopy (WLC). This assumption is tested in sensitivity analysis.		18. CSC_NMP22_WLC (CSC_WLC) 19. CSC_PDD (CSC_WLC) 20. CSC_NMP22_PDD (NMP22_WLC) 21. CSC_IMM_WLC (CSC_WLC) 22.CSC_CTL_PDD (CSC_WLC) 23. CSC_IMM_PDD (IMM_WLC) 24. CSC_FISH_PDD (CSC_WLC) 25. CSC_NMP22_PDD (CSC_WLC) 26. CSC_IMM_PDD (CSC_WLC)	that they considered to be important. One of the sensitivity analyses is of particular interest because it involved measuring effectiveness using QALYs (the effectiveness measure preferred by NICE). This was done by applying quality of life measures associated with other urological cancers. **<u>Cost-utility analysis</u>** **<u>Effectiveness (QALYs)</u>** 1. CTL_WLC (CTL_WLC) 2. CTL_PDD (CTL_WLC) 4. FISH_PDD (FISH_WLC) 8. IMM_PDD (IMM_WLC) 16. CSC_FISH_PDD (FISH_WLC) 19. CSC_PDD (CSC_WLC) 23. CSC_IMM_PDD (IMM_WLC) 26. CSC_IMM_PDD (CSC_WLC) **<u>Costs</u>** 1. CTL_WLC (CTL_WLC) 2. CTL_PDD (CTL_WLC) 4. FISH_PDD (FISH_WLC) 8. IMM_PDD (IMM_WLC) 16. CSC_FISH_PDD (FISH_WLC) 19. CSC_PDD (CSC_WLC)	 9.00 9.01 9.04 9.04 9.05 9.01 9.05 9.05 £1,043 £1,094 £1,235 £1,458 £2,005 £2,082	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	The relative risk (RR) of progression in bladder cancer patients not receiving treatment (false negative) compared with those receiving treatment (true positive) was assumed to be 2.56. This assumption is based on information from the study by Millán-Rodriguez et al. 2000 using a comparison of TURBT plus BCG versus TURBT alone. The authors made assumptions about the probability of detecting missed bladder cancer following false-negative results. It was assumed that the following proportions would be detected at each time point: First three months – 50% First year – 50% Second year – 75%			23. CSC_IMM_PDD (IMM_WLC) 26. CSC_IMM_PDD (CSC_WLC) **<u>ICER (cost per QALY)</u>** 1. CTL_WLC (CTL_WLC) 2. CTL_PDD (CTL_WLC) 4. FISH_PDD (FISH_WLC) 8. IMM_PDD (IMM_WLC) 16. CSC_FISH_PDD (FISH_WLC) 19. CSC_PDD (CSC_WLC) 23. CSC_IMM_PDD (IMM_WLC) 26. CSC_IMM_PDD (CSC_WLC) **Other one-way sensitivity analyses** Other one-way sensitivity analyses considered by the authors involved changes to the following parameters: Note that in the interest of brevity, not all results are presented here. Only the most cost-effective strategy is presented, using a threshold of £30,000 per life year. • **Bladder cancer prevalence rate** Prevalence = 1% Prevalence = 10%	£2,195 £2,370 - £4,678 £5,051 Extendedly dominated £66,905 Dominated Dominated Dominated CTL_PDD (CTL_WLC)	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	After second year – 100% **<u>Source of utility data:</u>** Not utilised in the base case because, according to the authors, no suitable QoL data could be sourced. However, the use of QoL values associated with other urological cancers was explored in sensitivity analysis. The majority of these values were based on a published decision analysis of management options in high risk bladder cancer (Kulkarni et al. 2007). **<u>Source of cost data:</u>** The costs associated with CSC, WLC, cytology, ImmunoCyt, FISH and WLC-assisted transurethral resection of bladder tumour (TURBT) were sourced from 2006			Prevalence = 20% • **Sensitivity and specificity of flexible cystoscopy** Sensitivity and specificity +5% Sensitivity and specificity +10% Sensitivity and specificity +25% • **RR of progression of bladder cancer comparing no treatment with treatment** RR = 2.00 RR = 1.50 RR = 1.00 • **RR of recurrence comparing PDD and WLC** RR = 0.90 RR = 0.80 RR = 0.64 • **RR of progression comparing**	CSC_FISH_PDD (FISH_WLC) CSC_IMM_PDD (IMM_WLC) IMM_PDD (IMM_WLC) IMM_PDD (IMM_WLC) CSC_PDD (CSC_WLC) FISH_PDD (FISH_WLC) FISH_PDD (FISH_WLC) CTL_WLC (CTL_WLC) IMM_PDD (IMM_WLC) IMM_PDD (IMM_WLC) IMM_PDD (IMM_WLC)	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	NHS reference costs. The additional cost of extra equipment, personnel and time associated with photodynamic diagnosis (PDD) were obtained from a business report prepared by Karl Storz (Endoscopy [UK], 2006, personal communication). It was assumed that PDD equipment lasts for five years and the average number of PDD test per year is 100. The cost of a computerised tomography (CT) scan was based on a previous HTA, which investigated diagnostic tests in the investigation of haematuria (Rodgers et al. 2006). The cost associated with			**PDD and WLC** RR = 0.90 RR = 0.80 RR = 0.56 • **Discount rate** 6% 1% 0% • **Proportions in each prognostic risk group in NMIBC patients** Low = 30%, high = 30% Low = 60%, high = 10% • **Starting age and time horizon** 57 years old 77 years old 10 year time horizon • **Follow up strategies** Second test in follow-up is PDD	IMM_PDD (IMM_WLC) IMM_PDD (IMM_WLC) IMM_PDD (IMM_WLC) FISH_PDD (FISH_WLC) IMM_PDD (IMM_WLC) IMM_PDD (IMM_WLC) IMM_PDD (IMM_WLC) IMM_PDD (IMM_WLC) IMM_PDD (IMM_WLC) FISH_PDD (FISH_WLC) FISH_PDD (FISH_WLC)	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	NMP22 was based on the marketing price in the UK (identified from MediChecks.com). Downstream costs associated with the treatment and management of cancer were also considered. The total cost of cystectomy and unit cost of palliative treatment were based on 2006 NHS reference costs. The cost of palliative treatment was estimated by multiplying the unit day cost by 135 days (estimation based on the opinion of clinical experts). The unit cost associated with radical radiotherapy was obtained from Aberdeen Royal Infirmary (Dr Nabi, University of Aberdeen, 2008, personal communication. This unit			**Probabilistic sensitivity analysis (PSA)** A PSA was performed to assess the uncertainty surrounding model parameters. Cost-effectiveness acceptability curves (CEACs) were used to present the results of the PSA. With the exception of strategy 1 [CTL_WLC (CTL_WLC)], none of the strategies are likely to be cost-effective when society is willing to pay relatively little for an additional life year. Four strategies each have approximately a 20% probability of being cost-effective over much of the thresholds; CTL-WLC (CTL-WLC), FISH-PDD (FISH-WLC), IMM-PDD (IMM-WLC) and CSC-FISH-WLC (FISH-WLC). As well as performing a PSA on the base case analysis (above), the authors also conducted a PSA on the sensitivity analysis where QALYs are used as the effectiveness measure.	FISH_PDD (FISH_WLC)	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	cost was then multiplied by 35 sessions (reflecting that radical radiotherapy requires 30-40 sessions). The costs associated with three drug treatments; mitomycin, BCG and cisplatin were derived from the British National Formulary (BNF). **Currency unit:** UK pound sterling (£) **Cost year:** Not reported but most costs seem to be based on 2006 prices. **Discounting:** Annual rate of 3.5% for costs and benefits			The results were similar to the PSA in the base case in that none of the strategies are clearly preferred. However, three strategies have approximately a 20% probability of being cost-effective over much of the thresholds; CTL-WLC (CTL-WLC), FISH-PDD (FISH-WLC) and CSC-FISH-WLC (FISH-WLC). This differs from the PSA in the base case, where IMM-PDD (IMM-WLC) was also in this group (it now has around a 15% probability of being cost-effective over much of the thresholds).		

2.4 Imaging

2.4.1 Staging of the bladder and pelvic lymph nodes

Review question: In patients with new or recurrent bladder cancer is MRI more effective than CT for local staging and assessment of regional lymph nodes and can these tests be omitted in patients with NMIBC?

Rationale

Accurate staging of bladder cancer is important as tumour stage is key in determining the most appropriate treatment for an individual patient. Tumours are initially categorised as either muscle invasive or non muscle invasive, based upon histological analysis of specimens obtained at transurethral resection of the tumour. Non muscle invasive tumours are subcategorised as either high risk or low risk, dependent upon histological features. Low risk non muscle invasive disease makes up the largest group of patients with bladder cancer and these patients do not usually undergo any imaging staging (however, the evidence base for this requires review). Patients with muscle invasive or high risk non muscle invasive tumours have a higher risk of tumour extension beyond the bladder wall, of spread to adjacent organs, of lymph node involvement and of distant metastases and these patients require imaging staging. At present in the UK, initial tumour staging is performed almost exclusively with either CT or MRI. There is generally considered to be little difference in the accuracy of these modalities in terms of staging of the primary tumour (T staging).

Alternative imaging techniques for staging include PET/CT. The most commonly used PET tracer, 18F-FDG, is unsuitable for local staging of primary bladder tumours as the bladder wall is obscured by intense activity within the urine. However, 18F-FDG-PET/CT may be accurate in the diagnosis of nodal involvement or distant metastases. PET/CT using alternative tracers which are not excreted in the urine, such as 18F-choline, has been studied in the staging of bladder cancer, but these tracers are more expensive and not widely available. This review should establish the relative accuracy of CT and MRI in the staging of muscle invasive bladder cancer, particularly with regard to recent development in MRI technique, such as perfusion and diffusion imaging. The role of these imaging techniques as well as PET/CT should also be established in the restaging of patients with bladder recurrence under consideration for salvage cystectomy.

Question in PICO format

Populations	Test	Comparators	Outcomes
Low risk NMIBC High risk NMIBC MIBC	Pelvic CT	Pelvic MRI (including multi-parametric MRI) PET-CT No imaging (in NMIBC population only)	• Sensitivity and specificity * for - T3b or higher disease - T2 or higher disease - Local recurrence - Regional lymph node metastasis • Change in management • Overall survival • Progression free survival • Morbidity associated with the test procedure

*Compared to reference standard of histopathology of surgical specimens or clinical/radiological follow up when there is no surgery.

METHODS

Information sources

A literature search was also performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. A date limit of 1990 onwards was agreed due to significant improvements in the imaging technology, which will impact upon diagnostic accuracy.

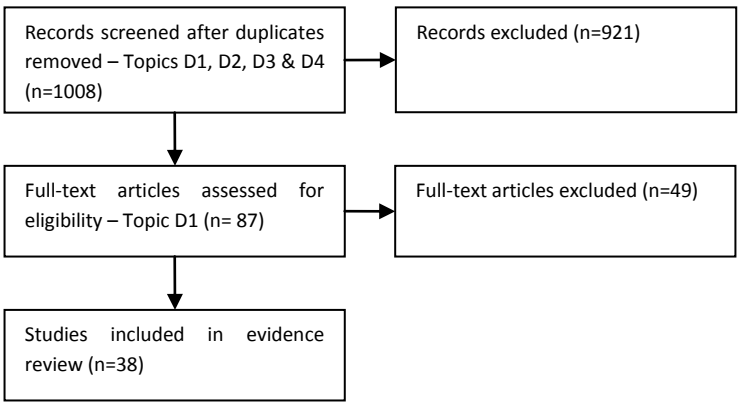
Data synthesis

Studies were presented according to outcomes reported. Due to heterogeneity across studies, diagnostic accuracy data could not be pooled. A narrative summary of the evidence is presented.

RESULTS

Result of the literature searches

Figure 19. Study flow diagram

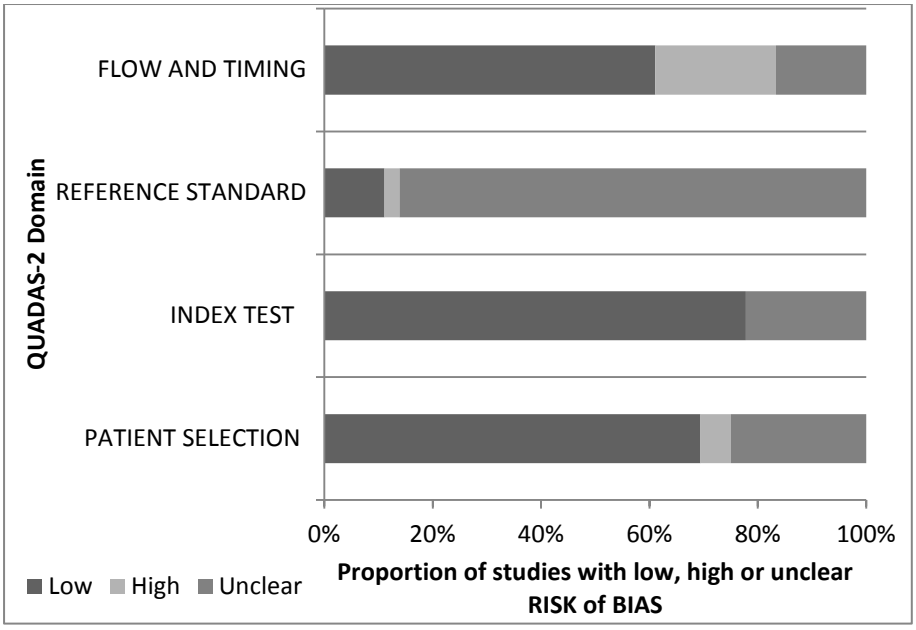


Study quality and results

The QUADAS-2 assessment tool was used to evaluate risk of bias in the 36 diagnostic accuracy studies. A majority of studies had a low risk of patient selection bias, as they recruited a consecutive or random sample of patients and avoided inappropriate exclusions. Most studies also reported that the index test (imaging) results were interpreted without knowledge of the reference standard (histopathology of surgical specimens or clinical/radiological follow-up) and reported diagnostic criteria. However, most studies did not report whether the reference standard was interpreted without knowledge of the index test results. 61% of studies were at low risk of 'flow and timing' bias. Some studies were classified as being at unclear or high risk as they did not report the interval between imaging and the reference standard, and in some studies not all patients received the same

reference standard (e.g. cystectomy or TURBT). The results of the QUADAS-2 assessment are provided in Figure 20.

Figure 20. QUADAS-2 risk of bias assessment results



Evidence statements

Staging accuracy

37 studies were identified and included in the evidence review. 36 studies reported the staging accuracy of CT, MRI or PET-CT. One study reported on the effect of PET-CT on the management of patients with muscle-invasive bladder cancer or high grade T1 bladder cancer. 18 studies provided data about the staging accuracy of CT and/or MRI (see Table 26). Four studies reported staging accuracy for both CT and MRI (Tachibana *et al.,* 1991; Kim *et al.,* 1994; Tanimoto *et al.,* 1992; Vargas *et al.,* 2012). Three of these studies reported more accurate T-staging with MRI, and one study of 16 patients reported no significant difference between CT and MRI (Vargas *et al.,* 2012). Across 28 studies, the staging accuracy of MRI ranged from 30% to 89%. Across five studies, the staging accuracy of CT ranged from 45% to 63%.

Sensitivity and specificity for T2 or higher

29 studies reported the sensitivity and specificity of the imaging modalities for detecting metastatic lymph nodes, or for distinguishing muscle invasive from non-muscle invasive bladder cancer (see Table 27). Tachibana *et al.* (1991) reported the sensitivity and specificity for classifying the presence or absence of muscle invasion in 57 patients (31 of whom had NMIBC) was 96% and 58% respectively for CT and 96% and 83% for enhanced MRI. Specificity was significantly higher with MRI. Takeuchi *et al.* (2009) reported tumour-based analysis of MRI for detecting Tis-T1 tumours from T2-

T4 tumours in 40 patients (23 with NMIBC). Specificity with T2WI plus DWI (100%) or all three image types together (100%) were better than that obtained with T2WI alone (74%). Sensitivity was not improved when DWI was used, with sensitivity of 88% for both T2WI and T2WI plus DWI and 94% for T2WI plus contrast enhancement. Six MRI studies reported patient-based analysis of sensitivity and specificity (see Figure 21). The proportion of patients with muscle invasive bladder cancer ranged from 17% to 54% across these studies. Sensitivity ranged from 68% to 100%, and specificity ranged from 73% to 92%. Data were not pooled due to heterogeneity across studies.

Sensitivity and specificity for T3b or higher

Kim *et al.* (1994) reported that when 36 patients were grouped as Ta-T3a and T3b-T4, the sensitivity and specificity for staging was 93% and 71% for CT and 86% and 73% for dynamic enhanced MRI. There were no significant differences in sensitivity and specificity between CT and MRI or between any of the MRI techniques (e.g. T1WI, T2WI, dynamic enhanced imaging and late enhanced imaging). Two CT studies with 167 patients in total reported the accuracy of detecting perivesical invasion (Kim *et al.* 2004; Baltaci *et al.* 2008). The sensitivity and specificity was 89% and 95% in Kim *et al.* (2004) and 85% and 63% in Baltaci *et al.* (2008). Five MRI studies reported the diagnostic accuracy of distinguishing T2 or lower from T3 or higher bladder cancer (Daneshmand *et al.*, 2012; Rajesh *et al.*, 2011; Tekes *et al.*, 2005; Wu *et al.*, 2013; Ghafoori 2013). Sensitivity ranged from 77% to 93% and specificity ranged from 60% to 95% across studies.

Sensitivity and specificity for regional lymph node metastases

See Figures 22 and 23. Data were not pooled due to heterogeneity across studies. The prevalence of metastatic pelvic lymph nodes varied across studies, which could be caused by variations in patient populations or variation in the number of lymph nodes removed at surgery. The prevalence of metastatic lymph nodes ranged from 17% to 53% in the five FDG PET-CT studies, from 13% to 45% across the eight CT studies and from 13% to 33% across the seven MRI studies. For FDG PET-CT, sensitivity ranged from 33% to 70% and specificity ranged from 87% to 100% across five studies. For CT, sensitivity ranged from 9% to 75% and specificity ranged from 56% to 100% across eight studies. For MRI, sensitivity ranged from 0% to 86% and specificity ranged from 71% to 100% across seven studies. Two studies reported the detection of metastatic lymph nodes with C-choline PET-CT with sensitivity of 58% and 63% and specificity of 66% and 100% reported by Maurer *et al.* (2012) and Picchio *et al* (2006) respectively. One study reported node-based detection of DW contrast enhanced MRI with a sensitivity of 76% and specificity of 89% (Papalia *et al.* 2011). Deserno *et al.* (2004) reported node-based detection in 172 nodes with Ferumoxtran-10 MRI. The pre-contrast and post-contrast sensitivities were 76% and 96% respectively. The pre-contrast and post-contrast specificities were 97% and 95%, respectively. Schoder *et al.* (2012) reported nodal-based detection for C-acetate PET-CT, with sensitivity of 100% and specificity of 87%.

Change in management

Mertens *et al.* (2013) compared treatment decisions before and after PET-CT. In 96 patients PET-CT was performed after conventional staging with CT scans of the abdomen and chest. PET-CT upstaged 20% of patients. Treatment recommendations changed in 13/96 (13.5%) patients after

PET-CT imaging. Treatment changed in 6/47 patients from direct cystectomy to neoadjuvant chemotherapy based on additional lesions seen at PET-CT. All lesions were confirmed by fine-needle aspiration. 7/82 patients changed from curative treatment to palliative management. Five patients did not follow post-FDG-PET treatment due to poor performance status, comorbidities or refusal of therapy.

Table 26: Accuracy of T-staging by imaging modality (% of tumours understaged, overstaged and accurately staged by imaging)

RC, radical cystectomy; TUR, transurethral resection; CE CT, contrast-enhanced CT; NR, not reported; Gd-CE, Gadolinium-contrast enhanced MRI; MDCT, Multi-detector CT;

Study	Total N patients	Ref standard (N)	Type of CT	N CT stage / N Pathological stage						No. (%) under-staged	No. (%) over-staged	No. (%) accurately staged	Type of MRI	N MRI stage / N Pathological stage						No. (%) under-staged	No. (%) over-staged	No. (%) accurately staged
				Ta	T1	T2	T3a	T3b	T4					Ta	T1	T2	T3a	T3b	T4			
Tachibana 1991	57	TUR (26)	CE CT	13/26						7 not detected	6 (23)	13 (50)	Gd-CE	22/26						1 not detected	4 (15)	22 (85)
		RC (31)		1/5		5/11	2/6	5/7	1/2	6 (19)	10 (32)	14 (45)[1]		3/5		7/11	4/6	4/7	2/2	5 (16)	6 (19)	20 (65)
Kim 1994	36	TUR (14) RC (22)	CE CT	0/3		3/7	0/2	10/12	3/4	3 (10)	10 (34)	16/29 (55)	T1W	0/3		0/9	2/4	9/12	5/6	8 (22)	12 (33)	16 (44)
													T2W	1/3		4/9	2/4	10/12	5/6	5 (14)	9 (25)	22 (61)
													Gd-CE	1/3		3/6	1/2	9/10	4/4	2 (7)	7 (26)	18(67)
													Late Gd-CE	1/3		3/9	2/4	10/12	6/6	1 (3)	12 (33)	23 (64)
Tanimoto 1992	86 tumour	TUR (47) RC (32)	CE CT	26/54		5/9	3/6	8/11	5/6	5 (6)	23 (27)	47 (55)[2]	Gd-CE	33/54		8/9	4/6	10/11	6/6	3 (3)	5 (6)	73 (85)[3]
													Conventional MRI	33/54		2/9	3/6	7/11	5/6	9 (10)	18 (21)	50 (58)[4]
Vargas 2012	16	All RC	CE CT	-		-	-	-	-	1 (6)	5 (31)	10 (63)	Gd-CE	-		-	-	-	-	1 (6)	6 (38)	9 (56)
Tritschler 2012a	276	RC	MDCT	63/114				29/96	18/46	30%	17%	51%										
Rajesh 2011	100	All TUR											Gd-CE phased array body coil	32/55		28/40	-	2/3	1/2	13 (13)	24 (24)	63 (63)
Daneshmand 2012	122	All RC											Dynamic Gd-CE	T0 2/14	4/28	23/38		12/27	8/15	29 (27)	31 (29)	47 (44)
Tekes 2005	71	unclear											Gd-CE phased array pelvic coil	16/24		6/10		11/21	7/6	4 (6)	23 (32)	44 (62)
Neuerberg 1991	68	TUR (47) RC (13) Biopsy (8)											Gd-CE	6/31		5/11		5/6	8/9	14 (25)	19 (33)	24 (42)
	26												T1W+T2W	0/13		1/3		3/3	3/4	5 (22)	11 (48)	7 (30)

Study	Total N patients	Ref standard (N)	Type of CT	N CT stage / N Pathological stage						No. (%) under-staged	No. (%) over-staged	No. (%) accurately staged	Type of MRI	N MRI stage / N Pathological stage						No. (%) under-staged	No. (%) over-staged	No. (%) accurately staged
				Ta	T1	T2	T3a	T3b	T4					Ta	T1	T2	T3a	T3b	T4			
Narumi 1993	50	TUR (33) RC (17)											T1W Gd-CE	28/33		3/4	3/5	3/5	2/3	4 (8)	7 (14)	39 (78)
													Oblique T2W	21/33		2/4	3/5	3/5	1/3	5 (10)	15 (30)	30 (60)
Liedberg 2013	47	RC											Gd-CE T1 and T2	-		-	-	-	-	6 (13)	23 (49)	18 (38)
El-Assmy 2009	106	TUR											DWI	21/33		25/33	30/32		7/8	3 (3)	20 (19)	83 (78)
													T2W	1/33		8/33	25/32		7/8	8 (8)	56 (53)	42 (40)
Barentsz 1996	49	RC (57) TUR (4)											Unenhanced T1+T2	8/10			7/10	11/14	11/15	9 (18)	3 (6)	37 (76)
													Unenhanced T1+T2+DWI	5/10			9/10	12/14	14/15	7 (14)	2 (4)	40 (82)
Ghafoori 2013	108 tumour	TUR (10) RC (76)											T1+T2 CE	0/1	8/10	37/42	26/32		23/23	6 (6)	8 (7)	94 (87)
Watanabe 2009	19	TUR (10) RC (8)											T1+T2	-	-	-	-		-	5 (26)	4 (21)	10 (53)
													T1+T2+Gd-CE	-	-	-	-		-	5 (26)	3 (16)	11 (58)
													T1+T2+DWI	-	-	-	-		-	5 (26)	1 (5)	13 (68)
Nishimura 2009	27	RC											1.5-T	-	-	-	-		-	4 (15)	7 (26)	16 (59)
Persad 1993	53	TUR (30) RC (25)											0.5-T T1+T2	18/18			18/22		11/13	2 (4)	4 (4)	47 (89)
Scattoni 1996	48	TUR (25) RC (23)											T1WI	14/25		-	3/9	10/11	1/1	2 (4)	18 (38)	28 (58)
													T2WI	17/25		2/2	4/9	10/11	1/1	2 (4)	12 (25)	34 (71)
													Gd-CE	21/25		1/2	6/9	10/11	1/1	1 (2)	8 (17)	39 (81)
													Late Gd-CE	11/25		-	5/9	10/11	1/1	1 (2)	20 (42)	27 (56)

[1] 1 pT2 tumour not detected by CT; [2] 11 pT1 tumours not detected by CT; [3] 5 pT1 tumours not detected by Gd-CE MRI; [4] 9 pT1 not detected by conventional MRI

Table 27: T staging and Lymph node staging sensitivity and specificity

RC, radical cystectomy; TUR, transurethral resection; CE CT, contrast-enhanced CT; NR, not reported; Gd-CE, Gadolinium-contrast enhanced MRI; MDCT, Multi-detector CT;

Study	Total N patients	Outcome	Pathology staging (No. pN+)	CT staging (%)					MRI staging (%)				
				Type of CT	Sensitivity	Specificity	PPV	NPV	Type of MRI	Sensitivity	Specificity	PPV	NPV
Tachibana 1991	57	≤T1 versus ≥T2	31 RC, 26 TUR	CE CT	96	58	71	93	Gd-CE	96	83	83	96
Kim 1994	36	Ta-T3a versus T3b-T4	22 RC, 14 TUR	CE CT	93	71	78	91	T1W	78	78	78	78
									T2W	83	78	79	82
									Gd-CE	86	73	80	80
									Late Gd-CE	86	100	72	78
Jensen 2011	18	LN detection	RC (3)	F-FDG PET/CT	33	93	50	88	T1+T2	0	80	0	80
Liedberg 2013	47	≤T2 versus ≥T3 or N+ LN detection	RC (8)	CE CT	86	42	55	79	3-T enhanced T1 and T2	86	31	50	73
										50	90	50	90
Vargas 2012	16	LN detection	RC (2)	CT	50	79	25	92	Gd-CE phased array body coil	50	71	20	91
				C-acetate PET/CT	100	71	33	100					
Daneshmand 2012	122	LN detection	RC (27)						Gd-CE	41	87	48	84
		≤T2N0 versus ≥T3N0								77	60	76	61
Takeuchi 2009	40 (52 tumours)	≤T1 versus ≥T2	17 RC 23 TUR						T2 weighted	88	74	63	93
									T2 plus DW	88	100	100	95
									T2 plus CE	94	86	76	97
									All image sets	94	100	100	97
		≤T2 versus ≥T3							T2 weighted	50	95	71	88
									T2 plus DW	70	97	88	93
									T2 plus CE	80	92	88	93
									All image sets	80	97	89	95
Rajesh 2011	100	≤T1 versus ≥T2	TUR						Gd-CE phased array body coil	78	93	94	78
		≤T2 versus ≥T3								91	60	98	25
Tekes 2005	62	≤T1 versus ≥T2	RC (10)						1.5-T GDE	97	67	77	96
		≤T2b versus ≥T3								86	84	77	90

Study	Total N patients	Outcome	Pathology staging (No. pN+)	CT staging (%)					MRI staging (%)				
				Type of CT	Sensitivity	Specificity	PPV	NPV	Type of MRI	Sensitivity	Specificity	PPV	NPV
		LN detection								70	98	88	95
Wu 2013	362	≤T1 versus ≥T2	NR						3-T T2W	87	73	57	93
									DW	89	91	80	95
									T2W+DW	92	98	95	97
	344	≤T2 versus ≥T3	RC						3-T T2W	81	91	67	96
									DW	85	95	79	97
									T2W+DW	89	97	87	98
Rosenkratz 2012	23	≤T1 versus ≥T2	16 Biopsy 7 RC						T2W	100	79	50	100
Kobayashi 2011	104	≤T1 versus ≥T2	TUR						DWI	66	91	81	82
									T2WI	68	91	81	83
Barentsz 1996	57	LN detection	RC (14)						Unenhanced T1+T2	71	98	91	91
									Unenhanced T1+T2+DWI	86	95	86	95
Ghafoori 2013	108 (tumours)	≤T1 versus ≥T2	10 TUR						T1+T2 contrast	98	82	98	82
		≤T2 versus ≥T3	76 RC						enhanced	93	94	94	93
Papalia 2011	72 (nodes)	LN detection	RC (34)						DWI GDE	76	89	87	71
Watanbe 2009	19	≥T2	10 TUR, 8 RC						T1+T2	80	79	57	92
									T1+T2+GDE	80	79	57	92
									T1+T2+DWI	40	93	67	81
Deserno 2004	172 (nodes)	LN detection	PLND (50)						Ferumoxtran-10 MRI - precontrast	76	97	97	91
									Ferumoxtran-10 MRI - postcontrast	96	95	89	98
Maeda 1995	26	≤T1 versus ≥T2	17 TUR 9 RC						0.5-T Unenhanced T1+T2	100	92	93	100
Persad 1993	24	LN detection	RC (5)						0.5-T Unenhanced T1+T2	63	100	100	84
Swinnen 2010	51	LN detection	RC (13)	CT	46	92	67	83					
				F-FDG PET/CT	46	97	86	84					
Picchio 2006	27	LN detection	RC (8)	CE CT	50	68	40	76					

Study	Total N patients	Outcome	Pathology staging (No. pN+)	CT staging (%)					MRI staging (%)				
				Type of CT	Sensitivity	Specificity	PPV	NPV	Type of MRI	Sensitivity	Specificity	PPV	NPV
				C-choline PET/CT	63	100	100	86					
Maurer 2012	44	LN detection	RC (12)	CE CT	75	56	39	86					
				C-choline PET/CT	58	66	39	81					
Kim 2004	67	Diagnosing perivesical invasion	RC	Dynamic CE CT	89	95	83	96					
Lodde 2010	44	LN detection	RC (13)	CE CT (n=33)	33	100	100	64					
				F-FDG PET/CT (n=44)	57	100	100	67					
Hitier-Berthault 2013	52	LN detection	RC (22)	CT	9	90	40	57					
				F-FDG PET/CT	36	87	67	65					
Tritschler 2012	243	LN detection	RC (72)	CT	30	90	58	74					
Baltaci 2008	100	LN detection	RC (13)	CT	31	94	44	90					
		Perivesical invasion			85	63	61	86					
Schoder 2012	109 (nodes)	LN detection	RC (3)	C-acetate PET/CT	100	87	18	100					
Kibel 2009	41	LN detection	RC (10)	FDG PET/CT	70	94	78	91					

Figure 21: Patient-based analysis of MRI for detecting non-invasive versus invasive bladder cancer

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kobayashi 2011 (T2W)	26	6	12	60	0.68 [0.51, 0.82]	0.91 [0.81, 0.97]
Watanabe 2009 (CE)	4	3	1	11	0.80 [0.28, 0.99]	0.79 [0.49, 0.95]
Wu 2013 (T2W)	91	69	14	188	0.87 [0.79, 0.93]	0.73 [0.67, 0.78]
Tachibana 1991 (CE)	25	5	1	25	0.96 [0.80, 1.00]	0.83 [0.65, 0.94]
Maeda 1995	14	1	0	11	1.00 [0.77, 1.00]	0.92 [0.62, 1.00]
Rosenkratz 2012 (T2W)	4	4	0	15	1.00 [0.40, 1.00]	0.79 [0.54, 0.94]

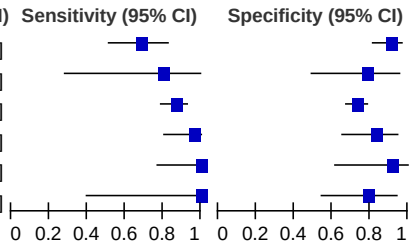
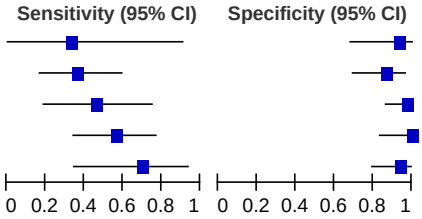


Figure 22: Patient-based analysis of PET-CT, CT and MRI for detecting lymph node invasion

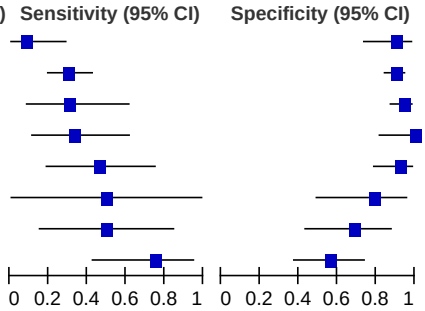
FDG PET/CT (LN detection)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jensen 2011	1	1	2	14	0.33 [0.01, 0.91]	0.93 [0.68, 1.00]
Hitier-Berthault 2013	8	4	14	26	0.36 [0.17, 0.59]	0.87 [0.69, 0.96]
Swinnen 2010	6	1	7	37	0.46 [0.19, 0.75]	0.97 [0.86, 1.00]
Lodde 2012	13	0	10	20	0.57 [0.34, 0.77]	1.00 [0.83, 1.00]
Kibel 2009	7	2	3	30	0.70 [0.35, 0.93]	0.94 [0.79, 0.99]



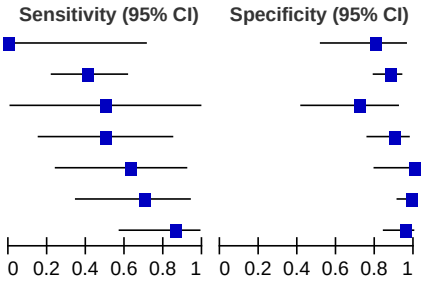
CT (LN detection)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hitier-Berthault 2013	2	3	20	27	0.09 [0.01, 0.29]	0.90 [0.73, 0.98]
Tritschler 2012	21	15	48	135	0.30 [0.20, 0.43]	0.90 [0.84, 0.94]
Baltaci 2008	4	5	9	82	0.31 [0.09, 0.61]	0.94 [0.87, 0.98]
Lodde 2012	5	0	10	18	0.33 [0.12, 0.62]	1.00 [0.81, 1.00]
Swinnen 2010	6	3	7	35	0.46 [0.19, 0.75]	0.92 [0.79, 0.98]
Vargas 2012	1	3	1	11	0.50 [0.01, 0.99]	0.79 [0.49, 0.95]
Picchio 2006	4	6	4	13	0.50 [0.16, 0.84]	0.68 [0.43, 0.87]
Maurer 2012	9	14	3	18	0.75 [0.43, 0.95]	0.56 [0.38, 0.74]



MRI (LN detection)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jensen 2011	0	3	3	12	0.00 [0.00, 0.71]	0.80 [0.52, 0.96]
Daneshmand 2012	11	12	16	83	0.41 [0.22, 0.61]	0.87 [0.79, 0.93]
Vargas 2012	1	4	1	10	0.50 [0.01, 0.99]	0.71 [0.42, 0.92]
Liedberg 2013	4	4	4	35	0.50 [0.16, 0.84]	0.90 [0.76, 0.97]
Persad 1993	5	0	3	16	0.63 [0.24, 0.91]	1.00 [0.79, 1.00]
Tekes 2005	7	1	3	60	0.70 [0.35, 0.93]	0.98 [0.91, 1.00]
Barentsz 1996	12	2	2	41	0.86 [0.57, 0.98]	0.95 [0.84, 0.99]



C-Choline PET/CT (LN detection)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Maurer 2012	7	11	5	21	0.58 [0.28, 0.85]	0.66 [0.47, 0.81]
Picchio 2006	5	0	3	19	0.63 [0.24, 0.91]	1.00 [0.82, 1.00]

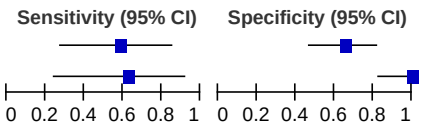
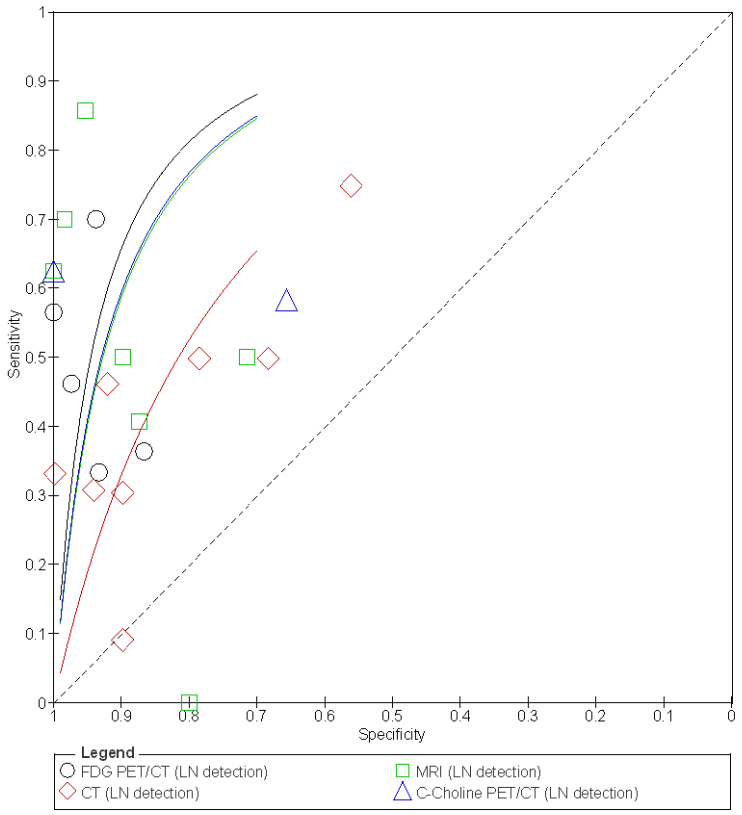


Figure 23. Summary ROC Plot of tests for metastatic lymph node detection: 1 FDG PET/CT, 2 CT, 3 MRI, 4 C-Choline PET/CT



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Reason: expert review

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Reason: outcomes not relevant to PICO

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Reason: population not relevant (colorectal cancer)

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Reason: technical note

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Golan, S et al. Comparison of 11C-choline with 18F-FDG in positron emission tomography/computerized tomography for staging urothelial carcinoma: a prospective study. Journal of Urology 2011; 186(2): 436-441.

Reason: outcomes not relevant to pico

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Reason: not relevant to PICO (not staging)

El-Assmy, A et al. Diffusion-weighted MR imaging in diagnosis of superficial and invasive urinary bladder carcinoma: A preliminary prospective study. Thescientificworldjournal 2008; 8: 364-370.

Reason: not relevant to PICO (not staging)

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Reason: does not assess imaging accuracy

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Reason: does not assess imaging accuracy

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Reason: pre-1990 (not relevant to current practice)

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Reason: non-systematic review

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Reason: outcomes not relevant (no staging data)

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Reason: pre-1990 (not relevant to current practice)

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Reason: comment

Lawrentschuk, N, Lee, ST, and Scott, AM. Current role of PET, CT, MR for invasive bladder cancer. [Review]. Current Urology Reports 2013; 14(2): 84-89.

Reason: expert review

Cowan, NC and Crew, JP. Imaging bladder cancer. [Review]. Current Opinion in Urology 2010; 20(5): 409-413.

Reason: expert review

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Reason: pre-1990 (not relevant to current practice)

Barentsz, JO et al. Primary staging of urinary bladder carcinoma: the role of MRI and a comparison with CT. [Review] [49 refs]. European Radiology 1996; 6(2): 129-133.

Reason: expert review

Saokar, A et al. Detection of lymph nodes in pelvic malignancies with Computed Tomography and Magnetic Resonance Imaging. Clinical Imaging 2010; 34(5): 361-366.

Reason: outcomes not relevant to PICO (no reference standard)

Paik, ML et al. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. Journal of Urology 2000; 163(6): 1693-1696.

Reason: not relevant to PICO (reviewed medical records not images)

Roy, C et al. Small pelvic lymph node metastases: evaluation with MR imaging. Clinical.radiology 1997; 52(6): 437-440.

Reason: 0.5 Tesla

Laval-Jeantet, M et al. MRI of the pelvis in comparison with CT scan. Archives Internationales de Physiologie et de Biochimie 1985; 93(5): 61-66.

Reason: pre-1990 (not relevant to current practice)

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Reason: not relevant to PICO – retrospective review of imaging report

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Reason: outcomes not relevant to PICO

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Reason: relevant outcomes not reported (no raw data, specificity not reported)

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Reason: outcomes not relevant to PICO (distant mets)

Kim, CS et al. Clinical significance of bladder urothelial thickening and enhancement revealed on MDCT urography after transurethral resection of tumor. Journal of Computer Assisted Tomography 2012; 36(2): 243-248.

Reason: outcomes not relevant to PICO

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Reason: outcomes not relevant to PICO

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Reason: not relevant to current practice (0.2Tesla)

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Reason: not relevant to PICO

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Reason: not relevant to PICO

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Reason: not relevant to PICO

Yang, Z et al. Clinical value of whole body fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in the detection of metastatic bladder cancer. International Journal of Urology 2012; 19(7): 639-644.

Reason: not relevant to PICO

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Reason: not relevant to PICO

Hwang, EC et al. Accuracy and factors affecting the outcome of multi-detector computerized tomography urography for bladder tumors in the clinical setting. Korean Journal of Urology 2011; 52(1): 13-18.

Reason: not relevant to PICO

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Reason: abstract only

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Reason: outcome not relevant to PICO (detection rather than staging)

Vargas, HA et al. Re: Prospective Evaluation of MRI, C-11-Acetate PET/CT and Contrast-Enhanced CT for Staging of Bladder Cancer Editorial Comment. Journal of Urology 2013; 190(5): 1713-1713.

Reason: editorial

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Reason: comparison not relevant to PICO (all patients had PET-CT)

Bashir, U et al. Diagnostic Accuracy of High Resolution MR Imaging in Local Staging of Bladder Tumors. J.Coll.Physicians Surg.Pak. 2014; 24(5): 314-317.

Reason: insufficient reporting of outcomes for inclusion

Brunocilla E., C. Diagnostic accuracy of 11C-choline PET/CT in preoperative lymph node staging of bladder cancer: A systematic comparison with contrast-enhanced CT and histologic findings. Clinical Nuclear Medicine 2014; 39(5): e308-e312.

Reason: insufficient reporting of outcomes for inclusion

Nguyen, HT. Improving bladder cancer imaging using 3-t functional dynamic contrast-enhanced magnetic resonance imaging. Investigative Radiology 2014; 49(6): 390-395.

Reason: outcomes not relevant to PICO (detection not staging)

Evidence tables

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
Jensen 2011 Denmark	Retrospective observational study	Low risk of bias, unclear if reference standard interpreted without knowledge of index tests.	18 with invasive BCa treated with RC. No distant mets. (30 patients undergoing staging were excluded as they did not receive RC due to distant mets or comorbidity)	14 male, 4 female. Mean age 65.4y (range 49-75). No T4 tumours	MRI (1.5 Tesla) of abdomen and pelvis. Whole body F-FDG PET/CT using STE PET/CT scanner immediately after urinating. PET after contrast-enhanced CT. In 17/18 cases both scans within 2 wks of each other. For MRI, LNs were evaluated in basis of size, texture, morphology, intensity of signal. LNs longer than 1cm on long axis were metastatic. LNs shorter than 1cm, appearing round, and with signal intensity similar to intensity of tumour were evaluated as suspicious for malignant involvement.	Histopathological examination of cystectomy and LN specimens	**LN detection** **FDG PET/CT** TP 1 FP 1 TN 14 FN 2 **MRI** TP 0 FP 3 TN 12 FN 3	**FDG PET/CT** Sn 33 Sp 93 PPV 50 NPV 88 **MRI** Sn 0 Sp 80 PPV 0 NPV 80	Detection of LN malignant involvement, per-patient analysis
Tachibana 1991 Japan	Observational study (appears prospective)	Low risk of bias, unclear if reference standard interpreted without knowledge of index tests, not all patients received same ref standard but these were reported separately.	57 patients with BCa before RC (31) or TUR (26). Patients having TUR limited to those with mean follow-up of 20.4 mo with no evidence of MIBC during f/up.	Not reported. 31/57	Gadolinium (Gd)-DPTA enhanced MRI (1.5 Tesla) fast-spin echo technique. T1 and T2-weighted. CT (GE 9800 scanner). The examination covered area between symphysis pubis and iliac crests. I.v. injection of urographic contrast after conventional scanning, followed by additional serial scans. Patients restricted from urinating 2hrs before scan. Imaging before biopsy and/or TUR. Image review was blinded to final pathologic results.	TUR (inc muscle layer and biopsies from base of resected area) or RC within 3 wks after imaging. No neoadjuvant CT or RT.	**CT**: accurate staging 27/57 (47%), understaged 11%, overstaged 28% Ta/T1: 13/26 (50%) accurately identified (7 not detected, 6 overstaged) RC patients: 45% accurately diagnosed (1 T2 not detected) **MRI:** accurate staging 42/57 (74%), understaged 9%, overstaged 16% Ta/T1: 22/26 (85%) accurately identified (1 not detected, 3 overstaged) RC patients: 64.5% staged correctly (no missed tumours)	**Presence/absence of muscle invasion** **CT** TP 24 FP 10 TN 14 FN 1 Sn 96% Sp 58% PPV 71% NPV 93% **MRI** TP 25 FP 5 TN 25 FN 1 Sn 96% Sp 83% PPV 83% NPV 96%	Accuracy of T staging. Sensitivity and specificity refers to accuracy of imaging to stage MIBC from NMIBC. E.g. TP=positive for MIBC on imaging and pathology, TN=negative for MIBC on imaging and pathology.
Kim 1994	Prospective observational	Moderate risk of bias, CT and	36 with BCa diagnosed with	20 male, 16 female. Mean age 61y	CT (GE 9800 scanner or Somatom Plus S scanner). No voiding 4hr	TUR (deep biopsy) or RC 1-	**CT**: accurate staging 16/29 (55%),	Ta-T3a vs. T3b-T4	Sensitivity and specificity refers

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
USA	study	MR images interpreted blindly, unclear if reference standard interpreted without knowledge of index test. Not all patients had CT or Gd-CE MRI, not all patients had same reference standard	biopsy 3 wks before imaging. Planned treatment was RC (22) or TUR (14). 13/22 RC patients had TUR 2-21mo before imaging.	(range 32-83) TCC (n=33), squamous (n=2, adenocarcinoma (n=1)	before CT. Iodinated contrast i.v Omnipaque 300. Oral iodinated contrast 500ml 5% (Gastrografin). A pendunculated lesion =T1, sessile lesion=T2, sessile lesion with wall thickening but without perivesical invasion =T3a, lesion with irregular border and streaky areas of higher attenuation in perivesical fat=T3b, invasion of adjacent organs=T4. MRI (1.5T on GE Signa unit and Magnetom unit). T1 weighted spin echo (SE) and T2-weighted as conventional or fast SE. Gd-enhanced spoiled GRE images acquired. Late Gd-enhanced T1-weighted imaging performed immediately after dynamic imaging, with same parameters as those used for pre-contrast imaging. Pelvic phased-array multicoil used in 12 patients and a body coil used in 24 patients. Images interpreted blindly and prospectively. For T2 and CE MRI, an intact, low-signal intensity muscle layer at base of tumour=T1, an irregular inner margin of low signal intensity muscle layer=T2, disrupted low-signal intensity muscle layer without perivesical infiltration=T3a.	11 days (mean 5) after MRI	overstaging 10/29 (34%), **MRI:** accurate staging T1 weighted 16/36 (44%), T2-weighted 22/36 (61%), dynamic MRI 18/27 (67%), late enhanced 23/36 (64%). Overstaging 33%, 25%, 26%, 33%, respectively. None of the techniques reliably separated mucosal from muscle layer. Depth of muscle wall invasion (pT2 vs. pT3) was poorly demonstrated by all imaging. Accuracy of imaging increased with T stage.	**CT** TP 14 FP 4 TN 10 FN 1 Sn 93% Sp 71% PPV 78% NPV 91% **MRI (dynamic Gd-enhanced)** TP 12 FP 3 TN 8 FN 2 Sn 86% Sp 73% PPV 80% NPV 80%	to accuracy of imaging to stage groups Ta-T3a from T3b-4 – this improved staging accuracy from when each stage was considered separately. Distant mets not evaluated.
Vargas 2012 USA	Prospective observational study	Low risk of bias, CT and MR images interpreted blindly, unclear if reference standard interpreted without knowledge of	16 with confirmed BCa, planned RC and PLND. 4 previous BCG, 6 neoadj CT, 3 both, 3 neither	Male 100% pT0 6 (38%) pTa 0 pT1 3 (19%) pT2 2 (12%) pT3 2 (12%) pTis 3 (19%) N0 14 (88%) N1 2 (12%)	**MRI:** 1.5-Tesla using multichannel phased-array body coil. T1, T2, T1 CE 3D, Gadopentetate dimeglumine followed by saline flush. Contrast enhanced MRI performed pre-contrast, 20s, 70s and 180s after i.v. contrast administration. Criteria for bladder tumours: 1) low-to-intermediate T1 signal intensity, 2) intermediate T2 signal intensity, 3) enhancement on early phase	Pathology of cystectomy/PLND specimen Mean 15 days (range 3-31) between imaging and surgery	**Accurate T staging:** MRI (9/16, 56%), CT (10/16, 63%), **Overstaging:** MRI (6/16, 38%), CT (5/16, 32%) **Understaging:** MRI (1/16, 6%), CT (1/16, 6%) **PET uptake:** 9 patients	**Accurate LN staging: MRI** Sensitivity 50% (1/2), specificity 71% (10/14) **PET CT:** Sens 100% (2/2), spec 71% (10/14) **CT:** Sens 50% (1/2), spec 79% (11/14)	Staging accuracy was reduced for all imaging in patients with prior BCG and/or systemic chemotherapy. FDG PET, CT, MRI showed similar accuracy. Imaging results did not

<table>
<tr><th>Reference</th><th>Study type</th><th>Study quality</th><th>N patients</th><th>Patient characteristics</th><th>Test</th><th>Reference standard</th><th>Raw data for 2x2 table</th><th>Sensitivity, specificity, PPV, NPV (%)</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td>index test</td><td></td><td></td><td>postcontrast sequences.
PET CT (C-acetate) – administered i.v. Imaging with combined PET CT scanner early, intermediate and delayed. Uptake abnormal when located in bladder wall or lymph nodes and intensity greater than that of adjacent blood pool or normal gluteal muscle activity.
Contrast enhanced CT – on 16-detector helical scanner. With oral contrast 30 min before CT.</td><td></td><td>uptake within bladder wall, TP in 7. FP in 2. In 7 patients without C-acetate uptake in bladder wall, 5 were TN, 2 were FN</td><td></td><td>affect patient management</td></tr>
<tr><td>Tanimoto 1992

Japan</td><td>Observational study (appears prospective) 1989-1991</td><td>Low risk of bias. All images reviewed without knowledge of final pathologic results, unclear if reference standard interpreted without knowledge of index test, not all patients had same reference standard (not reported separately)</td><td>79 consecutive patients with elevated lesions and/or abnormal mucosa at cystoscopy</td><td>64 male, 15 female
Mean age 64 (range 37-92).
No recurrent patients. 32 had RC, 47 TURBT after imaging</td><td>CT scanning and MRI – imaging performed without previous cystoscopic biopsy because inflammatory processes and edema from the biopsy would prevent accurate tumour staging from images.
CT/T 9800 scanner. Contrast enhanced. 60/79 had CT before MRI. Pedunculated tumour=T1, sessile tumour=T2, sessile tumour with thickened wall=T3a and obliteration of the boundary between bladder wall and perivesical fat=T3b.
MRI 1.5T – all patients restricted from urinating 2 hrs before. T1-weighted SE imaging with 4 signals averaged and T2-weighted SE imaging with 2 signals averaged. Dynamic MR imaging before and after injection of gadolinium. When hypointense line was intact in the region underlying the tumour, lesions were considered to be T2 or less severe. When hypointense line was disrupted at the attachment of the tumour but without extension to the perivesical fat = T3a. Further information on perivesical extent obtained from T1WI. Staging with</td><td>Cystoscopic biopsy/TUR with muscle in specimen performed within 1 week before surgical treatment.</td><td>CT accuracy n (%)
<table><tr><th>stage</th><th>n</th><th>%</th></tr><tr><td>pTa/ T1</td><td>54</td><td>26 (48)</td></tr><tr><td>pT2</td><td>9</td><td>5 (55)</td></tr><tr><td>pT3a</td><td>6</td><td>3 (50)</td></tr><tr><td>pT3b</td><td>11</td><td>8 (73)</td></tr><tr><td>pT4</td><td>6</td><td>5 (83)</td></tr><tr><td>All</td><td>86</td><td>47 (55)</td></tr></table>Dynamic MRI accuracy n (%)
<table><tr><th>stage</th><th>n</th><th>%</th></tr><tr><td>pTa/ T1</td><td>54</td><td>45 (83)</td></tr><tr><td>pT2</td><td>9</td><td>8 (89)</td></tr><tr><td>pT3a</td><td>6</td><td>4(67)</td></tr><tr><td>pT3b</td><td>11</td><td>10 (91)</td></tr><tr><td>pT4</td><td>6</td><td>6 (100)</td></tr><tr><td>All</td><td>86</td><td>73 (85)</td></tr></table></td><td>Overstaging in pT1: conventional MRI (14/54, 26%), CT (17/54, 32%), dynamic MRI (4/54, 7%).

Understaging and overstaging in pT2-T4 was lowest with dynamic MRI. Understaging in invasive tumours (as pTa and pT1) was lower with dynamic MRI compared to conventional MRI or CT.
One patient with lymph node involvement (LN <1cm) not detected by CT or MRI</td><td>Accuracy of T staging – per tumour analysis (total 86 tumours)</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type</th><th>Study quality</th><th>N patients</th><th>Patient characteristics</th><th>Test</th><th>Reference standard</th><th>Raw data for 2x2 table</th><th>Sensitivity, specificity, PPV, NPV (%)</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>dynamic MRI assessed linear hypointensity of muscle layer e.g. T1 shows intact linear hypointensity, T2 shows irregular linear hypointensity, T3a shows disrupted and T3b show abnormal intensity in perivesical fat.</td><td></td><td>Conventional MRI accuracy n (%)
<table><tr><th>stage</th><th>n</th><th>%</th></tr><tr><td>pTa/ T1</td><td>54</td><td>33 (61)</td></tr><tr><td>pT2</td><td>9</td><td>2 (22)</td></tr><tr><td>pT3a</td><td>6</td><td>3(50)</td></tr><tr><td>pT3b</td><td>11</td><td>7 (64)</td></tr><tr><td>pT4</td><td>6</td><td>5 (83)</td></tr><tr><td>All</td><td>86</td><td>50 (58)</td></tr></table></td><td></td><td></td></tr>
<tr><td>Daneshmand 2012

USA</td><td>Prospective observational study</td><td>Low risk of bias, image review blinded, all received same reference standard,</td><td>122 with MIBC confirmed by TURBT. Distant mets on CT scan excluded.</td><td>72 male, 54 female. Mean age 67.8 (range 46-81) years.</td><td>Dynamic gadolinium enhanced MRI: 1.5-Tesla
An intact hypointense muscle layer at the base of the tumour=T1, disrupted hypointense line without perivesical fat infiltration =T2, lesion with irregular outer border with some areas of the same signal intensity of the tumour in the perivesical fat=T3, spread into adjacent organ = T4. Lymph nodes with longest axis ≥10mm were considered positive. MRI reviewed by 2 radiologists blinded to pathologic stage.
Mean interval between TURBT and MRI 40 days (range 14-70)</td><td>RC with external pelvic/iliac lymph node dissection.</td><td>Staging accuracy: 40/122 (47%). Understaging: 29/122 (27%); Overstaging: 31/122 (29%)

LN detection<table><tr><td>TP</td><td>11</td></tr><tr><td>FP</td><td>12</td></tr><tr><td>TN</td><td>83</td></tr><tr><td>FN</td><td>16</td></tr></table></td><td>≤T2N0 versus ≥T3N0<table><tr><td>accuracy</td><td>65</td></tr><tr><td>Sens</td><td>77</td></tr><tr><td>Spec</td><td>60</td></tr><tr><td>PPV</td><td>76</td></tr><tr><td>NPV</td><td>61</td></tr><tr><td>FN</td><td>12.5</td></tr><tr><td>FP</td><td>52.4</td></tr></table>LN detection<table><tr><td>Accuracy</td><td>80</td></tr><tr><td>Sens</td><td>41</td></tr><tr><td>Spec</td><td>87</td></tr><tr><td>PPV</td><td>48</td></tr><tr><td>NPV</td><td>84</td></tr><tr><td>FN</td><td>59.3</td></tr><tr><td>FP</td><td>8.5</td></tr></table></td><td>Accuracy of LN detection and distinguishing T2N0 from T3N0. Data extracted from reviewer 1. Interobserver agreement was fair.</td></tr>
</table>

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
Takeuchi 2009 Japan	Prospective observational study	Moderate risk of bias, image review blinded, 17 patients excluded whose tumours were not histologically confirmed invasive or not, not all same reference standard	40 consecutive patients with NMIBC or MIBC had MRI before TUR (52 tumours analysed)	34 male (age range 49-85 mean 70) 6 female (age range 63-85 mean 73)	MRI: 1.5-Tesla with body coil and phased array 5-channel sensitivity encoding cardiac coil. DW images obtained in axial and sagittal planes. Dynamic contrast enhanced images also obtained. Radiologists blinded to other information Low SI line was present =T1 or lower, low SI line disrupted focally in the region underlying the tumour=T2 or higher. On DWI – a thin, flat high SI area corresponding to the tumour or a high SI tumour with a low submocosal stalk or a thickened submucosa = T1 or lower. High SI tumour without a submucosal stalk and smooth tumour margin=T2. In all perivesical fat invasion =T3, adjacent organ or abdominal wall=T4	TURBT with muscle or RC (within 41 days of MRI)	**Tis-T1 versus T2-T4 (all image sets) (n=52)** TP 16 FP 0 TN 35 FN 1 **Tis-T2 versus T3-T4 (all image sets) (n=48)** TP 8 FP 1 TN 37 FN 2	**Tis-T1 versus T2-T4 (all image sets) (n=52)** Sn 94 Sp 100 PPV 100 NPV 97 **Tis-T2 versus T3-T4 (all image sets) (n=48)** Sn 80 Sp 97 PPV 89 NPV 95	Per-tumour analysis. T2W plus contrast enhanced and T2W plus DWI were better than T2 alone
Rajesh 2011 UK	Observational study (appears retrospective)	Moderate risk of bias, TUR as reference standard in all patients, some had MRI before and some after TUR, time between MRI and TUR not reported	100 consecutive patients with proven BCa. 16 had RC, 16 RT.	73 male, 27 female. Age range 55-95 yrs.	MRI performed at presentation. 1.5-Tesla MRI using 6-channel phased array body coil. Gd enhanced images also obtained. MRI images retrospectively reviewed blind to staging at TUR. MRI performed after biopsy or TURBT in 26/100 patients (between 5-81 days)	Histological diagnosis from TURBT – muscle present in specimen of 94/100 patients	**T-staging:** Accurately staged (63/100 63%), understaged (13/100, 13%), overstaged (24/100, 24%). GDE images improved staging in 3 patients	**≤T1 versus ≥T2** Sens 78 Spec 93 PPV 94 NPV 78 **≤T2 versus ≥T3** Sens 91 Spec 60 PPV 98 NPV 25	RC specimen not used for pathological staging. Raw 2x2 data for sensitivity and specificity not reported – unable to include in RevMan
Tritschler 2012a Germany	Retrospective review	Low risk of bias, images interpreted blindly, all received RC within 50 days of imaging	276 who had RC 2004-2008 and pre-op staging with MDCT	201 male, 75 female. Mean age 68.2y. RC for pT2 (n=167), recurrent pT1 (n=53) or Tis (n=39) or infiltration of bladder by extravesical tumour	Multi-detector row CT: original images reviewed by an experienced radiologist who was blind to all histo findings and clinical staging. Patients with a delay of >50 days between staging and surgery were excluded.	Pathological findings from surgical specimen	**T-staging:** Accuracy 51%, overstaging, 17%, understaging 30%		Poor agreement between reviewer and primary radiologist.

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
				(n=17).					
Tritschler 2012b Germany	Retrospective review		276 who had RC 2004-2008 and pre-op staging with MDCT	201 male, 75 female. Mean age 68.2y	Multi-detector row CT: original images reviewed by a experienced radiologist who was blind to all histo findings and clinical staging. Patients with a delay of >50 days between staging and surgery were excluded. LN positive in nodes with a short axis diameter of ≥10mm and LN negative in nodes with diameter < 10mm on CT	Pathological findings from surgical specimen	**LN staging** TP 21 FP 15 TN 135 FN 48	**LN staging** Sens 30 Spec 90 PPV 58 NPV 74	Same cohort as Tritschler 2012a.
Tekes 2005 USA	Retrospective review	Moderate risk of bias, patients received different reference standard, unclear which ref standard was used to calculate staging accuracy	71 consecutive patients free of distant mets	62 male, 9 female. Mean age 64 (range 38-88). 62 had TUR 7-165 days before MRI. After MRI treatment was RC (n=39), partial cystectomy (n=2), TUR (n=26), palliative RT (n=3). Treatment received within 150 days (mean 31) after MRI	MRI: 1.5-Tesla Gd-enhanced with phased array pelvic coil. An intact hypointense line = T1, an irregular inner margin of hypointense line=T2a, disrupted hypointense line without perivesical invasion =T2b, lesion with irregular shaggy border and streaky areas of same signal intensity of the tumour in perivesical fat=T3b, lesion extending into adjacent organ or wall =T4. LN positive if long axis was 10mm or more.	Pathologic confirmation (unclear if from TUR or RC)	**T-staging:** accuracy 44 (62%), overstaging 23 (32%), understaging 4 (6%) **LN staging** TP 7 FP 1 TN 60 FN 3	**≤T1 versus ≥T2** Sens 97 Spec 67 PPV 77 NPV 96 **≤T2b versus ≥T3** Sens 86 Spec 84 PPV 77 NPV 90 **LN staging** Sens 70 Spec 98 PPV 88 NPV 95	2x2 data for NMIBC v MIBC not reported – unable to include in RevMan. Data extracted from reviewer 1. Interobserver agreement was good. Sensitivity for LN detection reported as 78% in paper but calculated as 70% based on 2x2 data.

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
Swinnen 2010	Observational study - prospective	Low risk of bias, all received same ref standard, unclear if consecutive sample of patients	51 RC between 2004-2007. No distant mets	43 male, 8 female. Mean age 66 (range 48-82) T2 or higher or recurrent T1G3 (with or without CIS). 1 patient who had neoadjuvant CT was excluded.	FDG-PET/CT: patients asked to urinate one hr after tracer injection. 4 slice spiral CT of whole body performed, followed immediately by whole body PET. LNs with elevated FDG uptake were considered suspicious for malignancy regardless of LN size on CT	Histopathology from RC with extended PLND. Mean interval between PET/CT and surgery 23 days	**LN staging: FDG-PET/CT** TP 6 FP 1 TN 37 FN 7 **LN staging: CT** TP 6 FP 3 TN 35 FN 7	**LN staging: FDG-PET/CT** Sens 46 Spec 97 PPV 86 NPV 84 **LN staging: CT** Sens 46 Spec 92 PPV 67 NPV 83	LN detection per patient analysis
Picchio 2006	Observational study prospective	Low risk of bias, all had same ref standard, image review was blinded.	27 consecutive patients referred for RC and PLND. Excluded distant mets, previous RT, neoadjuvant CT, other secondary malignancies	Median age 69 (range 45-81). All staged with TURB, abdominal CT assessed LN mets, bone scintography to detect bone mets.	C-Choline PET with whole body PET scanners. Contrast-enhanced CT with Sensation 16 scanner after i.v. iodine contrast injection. Reviewers blinded to other results. Imaging performed mean 23 days after TURBT. LN mets considered when nodal enlargement >10mm in the long axis was depicted.	Histologic exam of surgical specimen. RC with PLND (mean 23.9 days after imaging)	**LN staging (PET/CT)** TP 5 FP 0 TN 19 FN 3 **LN staging (CT)** TP 4 FP 6 TN 13 FN 4	**LN staging (PET/CT)** Sens 63 Spec 100 PPV 100 NPV 86 **LN staging (CT)** Sens 50 Spec 68 PPV 40 NPV 76	LN detection. Accuracy of PET/CT better than CT at the LN level (not at bladder wall level)
Maurer 2012	Prospective observational study	Moderate risk of bias, unclear if image review was blind, not all patients	44 MIBC or high grade T1 scheduled for RC without neoadjuvant CT. No distant	Male 77%, female 23%. Median age 66.5 (range 44-84)	C-Choline PET with Sensation 16 Biograph PET/CT scanner. CT scan with contrast enhancement. Image reviewers noted any focally increased nonphysiologic Choline uptake, as well as LN size, shape and	Histologic exam of surgical specimen within mean 13.5 days (range 1-89)	**LN staging (PET/CT)** TP 7 FP 11 TN 21 FN 5	**LN staging (PET/CT)** Sens 58 Spec 66 PPV 39 NPV 81	LN staging. Not all patients underwent extended PLND.

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
		scheduled for RC could be included due to limited C-choline, not all had extended PLND	mets or concomitant cancer.		contrast enhancement suggesting metastases. 5-point scale used (1-2 positive for tumour; 3,4 or 5 negative for tumour)	after imaging. In 20 patients an extended PLND was performed	**LN staging (CT)** TP 9 FP 14 TN 18 FN 3	**LN staging (CT)** Sens 75 Spec 56 PPV 39 NPV 86	
Kim 2004	Observational study – appears prospective	Low risk of bias, image review blinded, unclear if inappropriate exclusions were avoided	67 who underwent RC due to MIBC, or too large tumours for TUR	51 male, 16 female. Mean age 63 (range 35-75). 18 patients had perivesical invasion on histologic examination. Others confined to bladder wall.	CT: 4-channel multi-detector row helical scanner, with oral barium sulphate suspension 1 hr prior to CT. Radiologists unaware of cystoscopic findings. CT imaging 1-31 days (mean 11) after TURBT Wall thickening without enhancement was not considered to be bladder cancer but residual inflammation after TURB. Only the presence or absence of perivesical invasion was determined – present when the interface between bladder cancer and perivesical fat was irregular or when bladder cancer showed overt growth beyond outer margin of bladder wall.	Histologic exam of surgical specimen (within 2 wks, mean 9 days, of imaging)	**Perivesical invasion (≤T3a versus ≥ T3b)** TP 16 FP 3 TN 54 FN 2 2 were understaged and 3 were overstaged as having invaded the perivesical fat.	**Perivesical invasion (≤T3a versus ≥ T3b)** Sens 89 Spec 95 PPV 83 NPV 96	Sensitivity and specificity for diagnosing perivesical invasion. Frequency of concordance between CT and histology was better if ≥7 days from TUR to CT
Mertens 2013	Retrospective observational study	Low – retrospective review of preferred treatment options before and after PET/CT	96 patients with MIBC or T1G3 and BCG failure. CECT imaging <4wks before PET/CT, before definitive treatment	Male 73, female 23. Mean age 65 (range 40-85)	FDG-PET/CT: performed after conventional staging with CECT scans of abdomen and chest Mean interval between CECT and PETCT 3 days.	n/a – study compared treatment decisions before and after PET/CT	**Change in management** PET/CT upstaged 20% of patients. After PET/CT treatment recommendations changed in 13/96 (13.5%) patients. 6/47 changed from direct RC to neoadjuvant CT based on additional lesions seen at PET/CT. All confirmed by fine-needle aspiration. 7/82 patients changed from curative treatment to palliative management. 5 patients did not follow post FDG/PET treatment because of poor performance status or comorbidities or refusing therapy. PET/CT detected 10 lesions suspicious for second primary malignancies not detected by CECT in 8 patients. In 4 of these curative		

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
							treatment changed to palliative treatment. 2 other patients required additional surgery.		
Lodde 2010	Observational study – appears prospective	Low risk of bias, unclear if image review was blinded, not all patients had CT + PET/CT, unclear if consecutive or random sample of patients was used.	44 MIBC scheduled to have RC with no neoadjuvant CT, 19 under follow-up after RC, 7 re-staging after CT for locally advanced and mets BC	13 female, 57 male. Mean age 67 (range 49-86). 39 primary UC, 4 primary epidermoid, 1 neuroendocrine, 12 associated primary prostate cancer.	Whole body FDG-PET/CT: using PET/CT integrated system. Images acquired 75min after injection with 333-407 MBq of FDG. CT with oral contrast material but without i.v. contrast medium. Images reviewed with fusion of CT and PET images. No catheterization required. Standard thoracic and adomino-pelvic CT scan and bone scintigraphy. Any LN >1cm considered positive. Some cases of <1cm but multiple were considered positive. SUVmax was determined. Lesions with FDG accumulation on a confirmed anatomical structure were considered positive.	Histopathology from bladder and PLN obtained at cystoprostatectomy or anterior pelvic exoneration. All but 2 patients had extended lymphadenectomy. Mean time CT and surgery=25.4 days, between PET and surgery =30 days	**LN detection (CT)** TP 5 FP 0 TN 18 FN 10 **LN detection** TP 13 FP 0 TN 20 FN 10 **(PET/CT)**	**LN staging (CT)** Sens 33 Spec 100 PPV 100 NPV 64 **LN staging (PET/CT)** Sens 57 Spec 100 PPV 100 NPV 67	33 had CT and PET/CT, 11 had only PET/CT.
Hitier-Berthault 2013	Prospective observational study	Low risk of bias, image review and histological exam were both blinded to other results, appears to be a consecutive sample	52 indicated for RC with PLND. T2+ or NMIBC refractory to BCG or high risk of progression. No neoadjuvant CT or RT.	44 male, 8 female. Mean age 63.7 (range 35-86). 20 (39%) history of NMIBC, 13 (65%) prior BCG therapy	CT: Unenhanced and contrast enhanced chest, abdomen, and pelvis CT. FDG-PET/CT: using hybrid apparatus, combining PET camera and helical CT. Pet acquired 60-90mins after i.v. injection of 5-6MBq of FDG/kg bodyweight. From head to proximal thighs. PET/CT images reviewed blinded to CT results. Mean interval between TUR and PET/CT = 47.4 days. PET/CT positive or negative regardless of number, size, location of positive LNs.	Histology of RC with PLND. Mean 29 days between PET/CT and surgery. PLND was extensive in 77%. 22 patients had LN metastases all with at least pT3.	**LN detection (CT)** TP 2 FP 3 TN 27 FN 20 **LN detection** TP 8 FP 4 TN 26 FN 14 **(PET/CT)**	**LN detection (CT)** Sens 9 Spec 90 PPV 40 NPV 57 **LN detection (PET/CT)** Sens 36 Spec 87 PPV 67 NPV 65	LN detection of PET/CT versus CT. Performance of PET/CT better for ≥36days interval between TUR and PET/CT, no prior BCG, tumour stage≤pT2, absence of vascular emboli
Baltaci 2008	Observational study (appears retrospective)	Low risk of bias, unknown interval between CT and cystectomy, no details of	100 consecutive patients with MIBC who had staging before RC	89 male, 11 female. Mean age 62.7y (range 37-83). All had TURBT. Majority of scans obtained before TURBT. If not, CT	Abdominal and pelvic CT images re-evaluated and interpreted by one uroradiologist for evidence of extravesical tumour extension or pelvic lymph node metastases without knowledge of final pathological results. LN >10mm	Histology of surgery specimen – RC with bilateral iliaco-obturator lymphadenectomy.	**Perivesical invasion** TP 35	**Perivesical invasion** Sens 86	Perivesical invasion and LN detection.

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
		CT imaging, image review blinded		scans at least 2 wks after TUR	considered positive.		FP 22 TN 37 FN 6 **LN detection (CT)** TP 4 FP 5 TN 82 FN 9	Spec 63 PPV 61 NPV 86 **LN detection (CT)** Sens 31 Spec 94 PPV 44 NPV 90	
Yang 2012	Observational study - retrospective	Moderate risk of bias, unclear if image review or ref standard was blinded, not all patients received same ref standard, interval between imaging and follow-up not reported.	35 consecutive patients with history of bladder cancer and treated with bladder preservation (23 TUR, 12 partial cystectomy)	28 male, 7 female. Median age 56 (range 35-96). Primary stage 0a/1 (n=8, 23%); 2/3 (n=20, 57%); 4 (n=7, 20%). 15 (43%) prior adjuvant CT, 2 (6%) prior adjuvant RT, 6 (17%) prior adjuvant CT+RT.	Whole body F-FDG PET/CT: Siemens biograph 16HR PET/CT scanner using Explora FDG_4. Routine scan 1h after administration of the tracer. Oral hydration – voiding- refilling was used. Two nuclear medicine physicians evaluated the images independently. Abnormal FDG uptake was defined as radiotracer accumulation thought to be outside of the normal anatomic structure. SUVmax for each lesion was calculated.	All lesions detected by PET/CT confirmed by biopsy. Serial imaging (CT or MRI) or other clinical examinations were performed for negative results.	**Recurrences:** TP 11 FP 3 TN 20 FN 1 Among the 11 TP, 5 patients were detected only after additional pelvic images. The other 6, additional pelvic images provided better contrast between lesions and concentration of tracer in the bladder.	**Recurrences:** Sens 92 Spec 87 PPV 79 NPV 95	Detection of local recurrence. No staging data.
Wu 2013	Observational study – appears prospective	Moderate risk of bias, reference standard unclear – not specified if TUR or RC, image review blinded to clinical and histological	362 consecutive patients with BCa who had histological exam through cystoscopy within 48 hrs after MRI.	306 male, 56 female. Mean age 71 years (range 48-87) Pathological stage: Tis-T1 (n=257, 71%); T2 (n=25, 7%); T3 (n=40, 11%); T4 (n=22, 6%)	MRI: 3.0-T with phased-array 8-channel cardiac coil. Patients had moderately distended bladder. T2WI, fat suppressed and DW images using single-shot spin echo echoplaner sequence. For all imaging TR and TE set to be as short as possible depending on number of sections and angle between body axis and imaging plane. Interpreted by 3 independent	All patients underwent surgery within 29 (mean 6) days after MRI. For TUR an additional deep muscle biopsy was performed at base of tumour. If no	**≤T1 versus ≥T2 (DWI)** TP 93 FP 23 TN 234 FN 12 **≤T1 versus ≥T2 (T2WI)** TP 91	**≤T1 versus ≥T2 (T2WI)** Sens 87 Spec 73 PPV 57 NPV 93 **≤T1 versus ≥T2 (DWI)** Sens 89	Data extracted from radiologist with intermediate level of experience (4yrs).

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
		findings, 18 tumours resected by TUR were classified as "T2 or higher" and not used for ≤T2 versus ≥T3 analysis			radiologists. On T2WI, the bladder wall was considered to be intact (T1 or lower) when the low SI line was present. T2 or higher when the low SI line was disrupted focally in the region underlying the tumour. On DW images, a thin flat high SI area corresponding to the tumour or a high SI tumour with a low SI submucosal stalk or thickened submucosa = T1 or lower, a high SI tumour without a submucosal stalk and with a smooth tumour margin = T2, extension into the perivesical fat = T3, extension into adjacent organs = T4.	tumour cells were detected, the pathologic stage was T1 or less.	FP 69 TN 188 FN 14 **≤T1 versus ≥T2 (T2WI+DWI)** TP 97 FP 5 TN 252 FN 8 **≤T2 versus ≥T3 (T2WI)** TP 50 FP 25 TN 257 FN 12 **≤T2 versus ≥T3 (DWI)** TP 53 FP 14 TN 268 FN 9 **≤T2 versus ≥T3 (T2WI+DWI)** TP 55 FP 8 TN 274 FN 7	Spec 91 PPV 80 NPV 95 **≤T1 versus ≥T2 (T2WI+DWI)** Sens 92 Spec 98 PPV 87 NPV 98 **≤T2 versus ≥T3 (T2WI)** Sens 81 Spec 91 PPV 67 NPV 96 **≤T2 versus ≥T3 (DWI)** Sens 85 Spec 95 PPV 79 NPV 97 **≤T2 versus ≥T3 (T2WI+DWI)** Sens 89 Spec 97 PPV 87 NPV 98	
Rosenkratz 2012	Retrospective observational study	Moderate risk of bias, unclear patient selection, not all received same	23 who had MRI following biopsy that was positive for BCa but without definitive	18 male, 5 female. Mean age 72 ±9 years (range 56-90)	MRI: protocol varied during study period 2003-2011. All on 1.5-T system, T2WI. All retrospectively reviewed by 2 radiologists who knew that initial pathology indicated non-invasive tumour, but were unaware of subsequent	Pathological specimen after MRI. Biopsy (16), cystectomy (7), 4 had muscle invasion on	**NMIBC versus MIBC** TP 4	**NMIBC versus MIBC** Sens 100 Spec 79 PPV 50 NPV 100	MRI protocol varied during study period. Prior to routine use of DWI

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
		reference standard, interval between imaging and ref standard unknown,	evidence of muscle invasion and also had 2nd histologic evaluation after MRI		pathological findings. Each classified for presence or absence of muscle invasion on multiplanar T2WI. For cases suspicious the radiologist classified a) disruption of T2-hypointense muscularis propria layer of bladder wall, b) perivesical fat stranding, c) perivesical soft tissue infiltration.	repeat tissue sampling. Of these 4, follow-up pathology was obtained with cystectomy in 3 and biopsy in 1 patient.	FP 4 TN 15 FN 0		
Neuerburg 1991	Observational study – appears prospective	Moderate risk of bias, patient selection unclear, not all received same ref standard, image review blinded, not all patients received same index test	68 with newly diagnosed (n=28) or restaging (n=40)	59 male, 9 female. Mean age 70 (range 42-87) Excluded patients without muscle in TURBT specimen. 18 prior TUR, 22 TUR+CT/CRT/RT	MRI: 1.5-T Magnetom and body coil. T1-weighted sequences before and after Gd-DPTA. T2-weighted before Gd-DPTA enhancement. Two radiologists were blinded to the histological diagnosis. T1-T3a – tumour confined to bladder wall, T3b – disruption of bladder wall, high signal perivesical fat interspersed with wispy areas of decreased signal intensity in nonenhanced scans, T4 – invasion of adjacent organs. MRI obtained before deep fractionated TUR.	TUR (n=47) 0-23 days after MRI, or radical/partial cystectomy (n=13) 3-43 days after MRI, or biopsy at laparotomy (n=8) 3-21 days after MRI	**Accuracy of staging with enhanced MRI (n=68):** Excluding stage pT0 (n=11) and with T1-T3a grouped together -accurately staged (24/57, 42%), overstaged (19/57, 33%), understaged (14/57, 25%) MRI overstaged 55% of pTa. If stage Ta-T3a were combined staging accuracy increases to 69%. **Accuracy of staging with plain T1 and T2W MRI (n=26):** Excluding stage pT0 (n=3) and with T1-T3a grouped together – accurately staged (7/23, 30%), overstaged (11/23, 48%), understaged (5/23, 22%)		Proton density and T2WI in 26 patients only, owing to difficulty for patients to prolonged examination times with filled bladder.
Narumi 1993 Japan	Prospective observational study	Moderate risk of bias, consecutive patients, not all patients had same ref standard, interval between imaging and ref standard unknown, not reported if image review was blind	50 consecutive patients with histologically proven BCa	45 male, 5 female. Mean age 63 (range 35-83)	MRI 1.5T Magnetom with double-surface coil. Bladder was mildly to moderately distended. T1W before and after Gd enhancement and oblique T2W images. Smooth band of low signal intensity at the base of the tumour =T1 or lower, irregular band of low signal intensity without disruption = T2, disrupted band of low signal intensity without irregular border contour=T3a, irregular outer bladder contour adjacent to an abnormal wall area=T3b, adjacent organ invasion=T4.	Histologic staging – TUR (33); RC (16) or partial cystectomy (1) with LND	**Accuracy of staging with Gd enhanced MRI:** Accurately staged (39/50, 78%), overstaged (7/50, 14%), understaged (4/50, 8%). **≤T1 versus ≥T2 = 90%** **≤T2 versus ≥T3a = 91%** **Accuracy of staging with oblique T2 MRI:** Accurately staged (30/50, 60%), overstaged (15/50, 30%), understaged (5/50, 10%). **≤T1 versus ≥T2 = 74%** **≤T2 versus ≥T3a = 88%** Accuracy of contrast-enhanced T1WI slightly higher than oblique T2WI for ≤T1 versus ≥T2 and ≤T2 versus ≥T3a but not significant		Unclear if image review was blind to other examination results.
Liedberg 2013	Observational study – prospective	Moderate risk of bias, unclear if consecutive	47 scheduled for RC and extended PLND.	34 male, 26 female. All had TURBT, CT of abdomen and chest, bimanual	MRI: after TURBT in 37 and before TURBT in 9 patients. 3.0-Tesla magnet Intera. Phased array cardiac coil. T2-weighted images and T1-	Histopathology from cystectomy specimen.	**Accurate staging MRI:** accurately staged (18/47, 38%), overstaged	**≤T2 versus ≥T3 or N+ (MRI) :** TP 18 FP 18	Staging accuracy not reported by pT stage 6 exclusions for

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
		sample, time between imaging and RC not reported, image results were re-evaluated by blinded uroradiologist.	Excluded distant mets.	palpation. 6 pT0, 4 pCIs, 3 pTa, 8 pT1, 2 pT2a, 3 pT2b, 9 pT3a, 6 pT3b, 6 pT4a	weighted precontrast and postcontrast images. MRI with 150ml sterile saline in bladder. CT: Philips CT scanner. Contrast enhanced of body including pelvis. All imaging re-evaluated by blinded uroradiologist. LN classification used RECIST criteria in both CT and MRI investigations.		(23/47, 49%), understaging (6/47, 13%) **LN staging MRI:** TP 4 FP 4 TN 38 FN 4 Sens 50 Spec 90 PPV 50 NPV 90	TN 8 FN 3 Sens 86 Spec 31 PPV 50 NPV 73 **≤T2 versus ≥T3 or N+ (CE CT) :** TP 18 FP 15 TN 11 FN 3 Sens 86 Spec 42 PPV 55 NPV 79	MRI outside protocol
Kobayashi 2011	Observational study - prospective	Low risk of bias, image review blinded, ref standard was TUR in all patients, unclear if ref standard was blinded	104 with cystoscopy proven BCa and/or +ve cytology had MRI before TUR	81 male, 23 female. Median age 68 (range 38-88) Ta (n=42, 40%); T1 (n=24, 23%), T2+ (n=38, 37%). N0 (n=98, 94%). M0 (n=100, 96%)	MRI: 1.5-T imager under free-breathing with 4-channel sensitivity encoding body coil. T2WI and DWI. 2 radiologists were blinded to TUR and histological findings. Diagnostic criteria was defined as a mass with a high signal intensity arising in the normal bladder wall with low SI DWI and a mass with intermediate SI arising in the low SI normal bladder wall on T2WMRI. A thin flat high SI area corresponding to the tumour or a high SI tumour with a low SI submucosal stalk or thickened submucosa, which resembles an inchworm = T1 or lower, a high SI tumour without submucosal components and with a smooth tumour margin =T2, a high SI tumour extended into perivesical fat and irregular margin=T3, extension into adjacent organs=T4	TURBT: repeat TUR of the tumour base was taken when histological reports mentioned submucosal but not muscular infiltration to avoid understaging MIBC as T1. Median time from MRI to TURBT was 17 days (range 2-68)	**≤T1 versus ≥T2 (DWI)** TP 25 FP 6 TN 60 FN 13 **≤T1 versus ≥T2 (T2W)** TP 26 FP 6 TN 60 FN 12	**≤T1 versus ≥T2 (DWI)** Sens 66 Spec 91 PPV 81 NPV 82 **≤T1 versus ≥T2 (T2W)** Sens 68 Spec 91 PPV 81 NPV 83	Data extracted from 1st reviewer. Interobserver agreement for detection was excellent for DWI and moderate for T2W. Staging accuracy was about 80% for both reviewers. T2W and DWI were comparable.
El-Assmy 2009	Observational study-prospective	Moderate risk of bias, image review	106 consecutive patients with	93 male, 13 female Mean age 59.4 (range 45-77).	MRI: 1.5-T with bladder moderately distended. T2W then DW images obtained under free breathing. 2	Final histopathology after TURBT	**Accuracy of staging:** DW-MRI (83/106, 78%, T2W-MRI (42/106, 40%) (p<0.001) Accuracy for staging ≤pT2 = 70% with DWI and		Accuracy of staging MRI prior to biopsy

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
		blinded, unclear for how many the ref standard was TUR or RC, interval between imaging and RC not reported	BCa on cystoscopy had MRI before cystoscopy and biopsy. Excluded contraindicatio n for MRI or cystoscopy	10 had multiple lesions. 72 had cystectomy, 26 TURBT and BCG, 8 radical radiotherapy.	radiologists were blinded to cystoscopy results. Discrepancies were resolved by consensus. Bladder tumours appeared on DWI as high signal intensity relative to the bladder wall and surrounding urine. Low signal intensity muscle layer at the base of the tumour=T1, mass with irregular inner margin and a disrupted low-signal intensity muscle layer without perivesical infiltration=T2, extension into perivesical fat=T3, invasion of adjacent organs=T4	within 48h of MRI or cystectomy specimen.	15% with T2W. Overstaging for ≤pT2 = 29% with DWI and 76% in T2W. Accuracy for staging >pT2 = 93% with DWI and 80% with T2W.		
Barentsz 1996	Observational prospective study	Low risk of bias, image review blinded, ref standard not blinded to imaging results, interval between MRI and ref standard not reported	61 consecutive patients with proven BCa had MRI 1-4 wks after TUR or biopsy.	47 male, 14 female. Mean age 61 (range 38-82). 2 had neoadjuvant CT after MRI. 42 subsequent curative cystectomy, 15 salvage/palliative cystectomy, 4 were undergoing 1-yr follow-up TUR.	MRI: 1.5-T with double surface coil. Initially 3D T1W magnetization-prepared rapid gradient echo (MP-RAGE) imaging was performed. T2W SE image also acquired in 10 patients. In remaining 51 a fast SE image was acquired. Gd enhancement images with single-section turbo fast low shot angle (turbo FLASH) sequence. Image review was blind to surgical results. Differentiation between tumour and postbiopsy tissue with unenhanced imaging was compared with differentiation with unenhanced plus turbo FLASH imaging. Also staging results were evaluated with both sets of images.	Histology at RC (57) or repeat TUR (4) – specimen sectioning for pathological evaluation performed on the basis of MRI findings	**Accuracy of T-staging:** Additional use of dynamic FLASH images improved overall staging results from (p<.01) Unenhanced T1+T2W accurate staged tumours excluding T0 = 76%, understaging = 18%, overstaging = 6% Unenhanced T1+T2W+DWI - accurate staged tumours excluding T0 = 82%, understaging = 14%, overstaging = 4%	**LN detection:** Unenhanced T1+T2W TP 10 FP 1 TN 42 FN 4 Sens 71 Spec 98 PPV 91 NPV 91 Unenhanced T1+T2W+DWI TP 12 FP 2 TN 41 FN 2 Sens 86 Spec 95 PPV 86 NPV 95	No difference in accuracy in those who had imaging 1 week versus 4 weeks after TUR. Interobserver variation 5%
Ghafoori 2013 Iran	Observational study prospective	Moderate risk of bias, unclear if image review was blinded, unclear if TUR	86 patients with BCa diagnosed by US, CT or MRI confirmed with cystoscopy	74 male, 12 female. Mean age 59.7 (range 32-86)	MRI: 1.5-T using pelvic phased-array coil. T2 and T1 weighted images breath-hold sequence before and after i.v. contrast medium. Staging by uroradiologist (unclear if blind to histology results).	Histopathology – RC (n=76) and TURBT (n=10)	**Accurate staging:** Accurately staged (94/108, 87%), understaged (6/108, 6%), overstaged (8/108,	**≤T1 versus ≥T2** Sens 98 Spec 82 PPV 98	Per tumour analysis. Raw 2x2 data for NMIBC/MIBC and organ confined/non

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
		included muscle in specimen, interval between MRI and ref standard not reported, not all patients received same ref standard			An intact hyposignal line (muscle layer) at the base of tumour=T1, irregular inner margin of the hyposignal line =T2a, disrupted hyposignal line without perivesical fat infiltration=T2b, lesion with irregular outer border and streaky areas of the same signal intensity of the tumour in the perivesical fat=T3b, extension into adjacent organ=T4.		7%)	NPV 82 **≤T2 versus ≥T3** Sens 93 Spec 94 PPV 94 NPV 93	organ confined not reported – unable to include in RevMan
Papalia 2011	Observational study - prospective	Low risk of bias, image review and histopathology blinded, interval between MRI and RC not reported.	36 consecutive patients with high grade MIBC. No nodal mets on CT scan. Excluded neoadjuvant CT	25 male, 11 female. Median age 72 (range 51-85)	DW-MRI: 1.5-T with spine array coil and body array coil. T1 and T2 weighted. Gadolinium based contrast medium used. Mean ADC value was 0.85 x 10^{-3} mm^3/s in the nodal metastatic group and 1 x 10^{-3} mm^3/s in the non-metastatic group. ADC cut-off value obtained from ROC curve was 0.86 x 10^{-3} mm^3/s. Conventional MR images were read blind to the DW image findings. The ADC measurement was performed in 72 nodal stations that showed a minimum of one nodal >5mm in diameter.	Histology from surgical specimen (RC with extended PLND). Pathologist blinded to DW-MRI results.	**LN detection based on ADC threshold from ROC curve:** TP 26 FP 4 TN 34 FN 8	**LN detection based on ADC threshold from ROC curve:** Sens 77 Spec 89 PPV 87 NPV 71	LN detection based on 72 nodal stations. Both index test and ref standard was blinded.
Watanabe 2009	Retrospective observational study	Moderate risk of bias, index test blinded, unclear if consecutive sample, unclear if TUR included muscle specimen, not all patients had same ref standard,	19 with known or suspected BCa who had MRI 6-30 days before treatment	18 male, 1 female. Mean age 71 (range 55-83). 3 had TUR before MRI 14 T1, 2 T2, 1 T3, 1 T4	MRI: 1.5-T, 4-channel sensitivity encoding body multicoil. T1 and T2 non-fat suppressed weighted. Gadolinium enhanced images also obtained. Three MR image sets were retrospectively reviewed. Unenhanced T1 and T2; unenhanced T1, T2-weighted and GDE images; unenhanced T1, T2 and DWI. Two independent radiologists blind to pathology results interpreted MRI. Muscle layer at the base of tumour	Histopathology of TUR (n=10), surgery (n=8)	**Staging accuracy:** T1/T2 53%; T1/T2/GDE 58%; T1/T2/DWI 68%	**T2 or greater** Sens 80 Spec 79 PPV 57 NPV 92 **T1+T2** **T1+T2+GDE**	Good agreement between radiologists.

<table>
<tr><th>Reference</th><th>Study type</th><th>Study quality</th><th>N patients</th><th>Patient characteristics</th><th>Test</th><th>Reference standard</th><th>Raw data for 2x2 table</th><th>Sensitivity, specificity, PPV, NPV (%)</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td>interval unclear</td><td></td><td></td><td>intact=T1, inner area of the muscle layer irregular=T2, muscle layer disrupted with or without perivesical fat infiltration=T3, tumour extension into adjacent organ or pelvic wall =T4.</td><td></td><td></td><td>T1+T2 +DWI
<table><tr><td>Sens</td><td>80</td></tr><tr><td>Spec</td><td>79</td></tr><tr><td>PPV</td><td>57</td></tr><tr><td>NPV</td><td>92</td></tr></table>
<table><tr><td>Sens</td><td>40</td></tr><tr><td>Spec</td><td>93</td></tr><tr><td>PPV</td><td>67</td></tr><tr><td>NPV</td><td>81</td></tr></table></td><td></td></tr>
<tr><td>Nishimura 2009</td><td>Retrospective observational study</td><td>Moderate risk of bias, unclear if consecutive sample, unclear if image review and pathologist was blinded, interval between MRI and cystectomy not reported,</td><td>27 who underwent total or partial RC for primary BCa.</td><td>21 males, 6 females. Mean age 67.5 ±8.8
Patients divided into 3 groups: a) CT after staging biopsy (n=8), b) CRT after staging biopsy (n=10), c) no neoadjuvant therapy (n=9)</td><td>MRI prior to TUR-biopsy and following neoadjuvant therapy: 1.5-T, bladder distended.
MRI T-stage following neoadjuvant therapy was compared to pathological T-stage</td><td>Histopathology of surgical specimen.</td><td colspan="2">Neoadjuvant CT was considered effective in 6 cases, in comparison of pre-treatment T stage and pathological T stage. Of these 6, 5 were overstaged by MRI.
Accuracy of MRI staging:
<table><tr><td></td><td>N (%)</td></tr><tr><td>Group A</td><td>6 (75)</td></tr><tr><td>Group B</td><td>3 (30)</td></tr><tr><td>Group C</td><td>7 (78)</td></tr><tr><td>Overall</td><td>16 (59)</td></tr></table>
Overstaging
<table><tr><td></td><td>N (%)</td></tr><tr><td>Group A</td><td>1 (13)</td></tr><tr><td>Group B</td><td>4 (40)</td></tr><tr><td>Group C</td><td>2 (22)</td></tr><tr><td>Overall</td><td>7 (26)</td></tr></table>
Understaging:
<table><tr><td></td><td>N (%)</td></tr><tr><td>Group A</td><td>1 (13)</td></tr><tr><td>Group B</td><td>3 (30)</td></tr></table></td><td></td><td>Retrospective study. Unclear if image reviewer and/or pathologist were blinded to other results.</td></tr>
</table>

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
							Group C 0 Overall 4 (15)		
Schoder 2011 USA	Prospective observational study	Low risk of bias, unclear if consecutive sample used, image review and pathology was blinded,	17 with TCC of the bladder scheduled for RC and extended bilateral PLND	17 males, 1 TisN0M0, 4 T1N0M0, 12 T2N0M0. 6 previous intravesical BCG on average 8mo prior to RC and PLND. Mean time from last TURBT to RC was 4 months (range 1-6).	C-acetate PET/CT ≤1 month prior to surgery. Findings were recorded prospectively but did not affect patient management. Standard PET scanner (n=2) or combined PET/CT system (n=15). 3 time points: immediately after injection, 20-40 mins post injection, and 40-60 mins post injection. Image review blinded. C-acetate uptake considered abnormal when located in LNs, bladder wall, or prostate gland, and of intensity greater than adjacent blood pool or normal gluteal muscle activity. SUV measured for abnormal uptake.	RC with PLND. 16/17 patients had RC 16±9 days after PET. 1 patient underwent exploration only due to unexpected extensive disease at surgery. Pathologist unaware of PET findings.	**LN detection:** TP 3 FP 14 TN 92 FN 0	**LN detection:** Sens 100% Spec 87% PPV 18% NPV 100%	LN detection for 109 nodal regions where histologic correlation was available - analysis per nodal region.
Deserno 2004	Prospective observational study	Low risk of bias, image review blinded, unclear interval between imaging and surgery, pathology not blinded to MRI results, not all nodes correlated with MRI findings	58 with proven bladder cancer were consecutively scheduled for RC. Excluded hemochromatosis, allergy to iron compounds, pregnant or breast feeding.	48 male, 10 female. Median age 60. 4% pT1, 20% pT2, 57% pT3, 19% pT4.	MRI with ferumtroxan-10 enhancement. TUR before MRI, mean interval 18 days (range 10-28). 1.5T with pelvic phased-array coil. Imaging performed before and 24-36 hours after i.v. infusion of Ferumoxtran-10, 2.6mg iron per kg of body weight. MR images using high spatial resolution 3D T1W and 2D T2W. Oval node considered metastatic if minimal axial diameter was greater than 8mm. On ferumoxtran-10 enhanced MR was metastatic if the entire node or focal area did not show a signal intensity decrease on T2WI.	PLND (n=44), image-guided biopsy (n=12), laparoscopic lymph node dissection (n=2). 50 nodes were positive at histopathology	**LN detection: pre-contrast MRI** TP 38 FP 1 TN 121 FN 12 **LN detection: post-contrast MRI** TP 48 FP 6 TN 116 FN 2	**LN detection: pre-contrast MRI** Sens 76 Spec 97 PPV 97 NPV 91 Sens 96 Spec 95 PPV 89 NPV 98 **LN detection: post-contrast MRI**	LN detection for 172 (43%) dissected nodes where histologic correlation was available - analysis per nodal region.
Kibel 2009 USA	Prospective observational study	Low risk of bias, unclear if consecutive or random sample used, not reported if image review	43 patients with cT2/T3N0M0 UCB with planned RC and PLND. No locoregional or	Median age 70 (range 32-87). Median follow-up 14.9 months.	PET/CT 60 mins after FDG. Foley catheter placed before FDG, furosemide i.v. 20mins after RDG, patients hydrated throughout. CT portion of study without contrast material. Attention directed to uptake of FGD in primary bladder	Pathology of surgical specimen (blinded to PET results). 41 patients had surgery mean	**LN detection:** TP 7 FP 2 TN 30 FN 3	**LN detection:** Sens 70 Spec 94 PPV 78 NPV 91	LN detection, per-patient analysis. Treatment altered by PET/CT in 2 patients (1 nodal metastasis had neoadjuvant CT, 1

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
		was blinded, pathology was blind to PET/CT, not all patients went on to have RC.	distant mets by CT/ bone scan. No prior CT or planned neoadjuvant CT		tumour, pelvic nodes, para-aortic nodes, and distant sites. Final consensus used as reflected in the clinical report. Maximum SUV of tumour foci determined.	8.6 days (range 2-36) after FDG-PET/CT.			widespread mets disease had palliative CT).
Maeda 1995 Japan	Retrospective observational study	Moderate risk of bias, consecutive sample used, unclear if index test and reference standard were blinded, not all patients received same ref standard.	26 consecutive patients	23 male, 3 female. Mean age 69.5 (range 46-96) 6 pTa, 6 pT1, 4 pT2, 3 pT3a, 7 ≥pT3a	MRI before TURBT. 0.5T. Bladder moderately distended. T1 and T2 weighted images acquired with 20cm field of view, a matrix size of 224x224 (pixel size 0.9mmx0.9mm) and a slice thickness of 7mm. Muscle invasion was considered present if disruption of the outer layer longer than 5mm was seen.	TURBT (n=17) or cystectomy (n=9) (1-50 days after MRI).	**Prediction of muscle invasion** TP 14 FP 1 TN 11 FN 0	**Prediction of muscle invasion** Sens 100 Spec 92 PPV 93 NPV 100	
Persad 1993 UK	Observational study – appears prospective	Moderate risk of bias, unclear if consecutive or random sample, unclear if imaging or ref standard blinded, unclear interval between index test and ref standard, not all received same ref standard	55 with bladder TCC	Not reported.	MRI: 0.5 Tesla Picker Vista scanner, Full bladder. Transverse multi-echo sequence giving proton density and T2 weighted images. Transverse STIR sequences used. Coronal T1 weighted SE sequence.	TUR and bimanual examination (n=30), cystectomy N=18), laparotomy (n=7) or autopsy (n=3)	**Staging accuracy:** 47/53 (89%) – excluding 2 T0. **LN detection (n=24)** TP 5 FP 0 TN 16 FN 3	**LN detection** Sens 63 Spec 100 PPV 100 NPV 84	Staging accuracy and LN detection (assume patient level)
Scattoni 1996 Italy	Prospective observational study	Moderate risk of bias, unclear if random or consecutive sample used,	48 with proven bladder cancer. Excluded history of TUR, IVT, CT or RT.	36 male, 12 female. Average age 62 (range 37-85) Diagnostic cystoscopy and cold cup biopsy at least	MRI: 0.5-Tesla. Bladder moderately distended. T1 and T2 . Field range of view 30-35cm Section thickness 7.5mm. Gd-enhanced images also acquired and delayed SE T1WI obtained when bladder filled with	RC (n=23) or TURBT (n=25) within 3 wks of MRI	**Accuracy of staging Ta-T1 versus T2-T4** T2WMRI: 36/48 (75%) T2WMRI:39/48 (81%) Gd-CE MRI: 44/48 (92%)		Patient level staging accuracy data

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
		image review blinded, not all patients received same reference standard		2 wks before MRI	contrast medium. Disruption of the hypointense line considered a sign of neoplastic infiltration.		Late Gd-CE MRI: 34/48 (71%)		

2.4.2 Detecting upper urinary tract involvement

Review question: In patients with new or recurrent bladder cancer is CT more effective than IVU for the detection of upper tract involvement and can these tests be omitted in patients with NMIBC?

Rationale

Intravenous urography has been replaced by CT in many areas of clinical practice, but is useful in the evaluation of the upper tracts. It may have a role to exclude ureteric obstruction and upper tract urothelial lesions, particularly in the low risk non-muscle invasive group. It would be useful to explore the comparative diagnostic accuracy of CT and IVU in the detection of tumours in the upper tract.

Question in PICO format

Populations	Test	Comparators	Outcomes
Low risk NMIBC High risk NMIBC MBIC	CT	IVU, No imaging (in NMIBC population only)	• Sensitivity and specificity * for presence of tumour in upper urinary tract • Change in management • Overall survival • Progression free survival • Morbidity associated with the test procedure

*Compared to reference standard of histopathology of surgical specimens or clinical/radiological follow up when there is no surgery.

METHODS

Information sources

A literature search was also performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

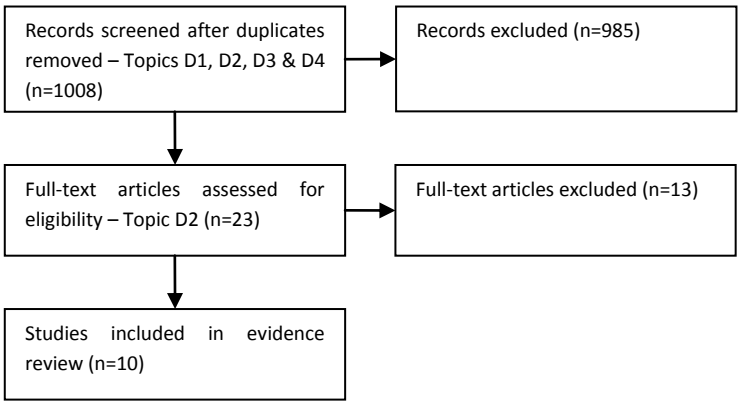
Data synthesis

A meta-analysis was not possible for this review question. The evidence is presented for the studies reporting sensitivity and specificity of the imaging techniques. Seven further studies reported the incidence of upper urinary tract tumours at bladder cancer diagnosis or during follow-up.

RESULTS

Result of the literature searches

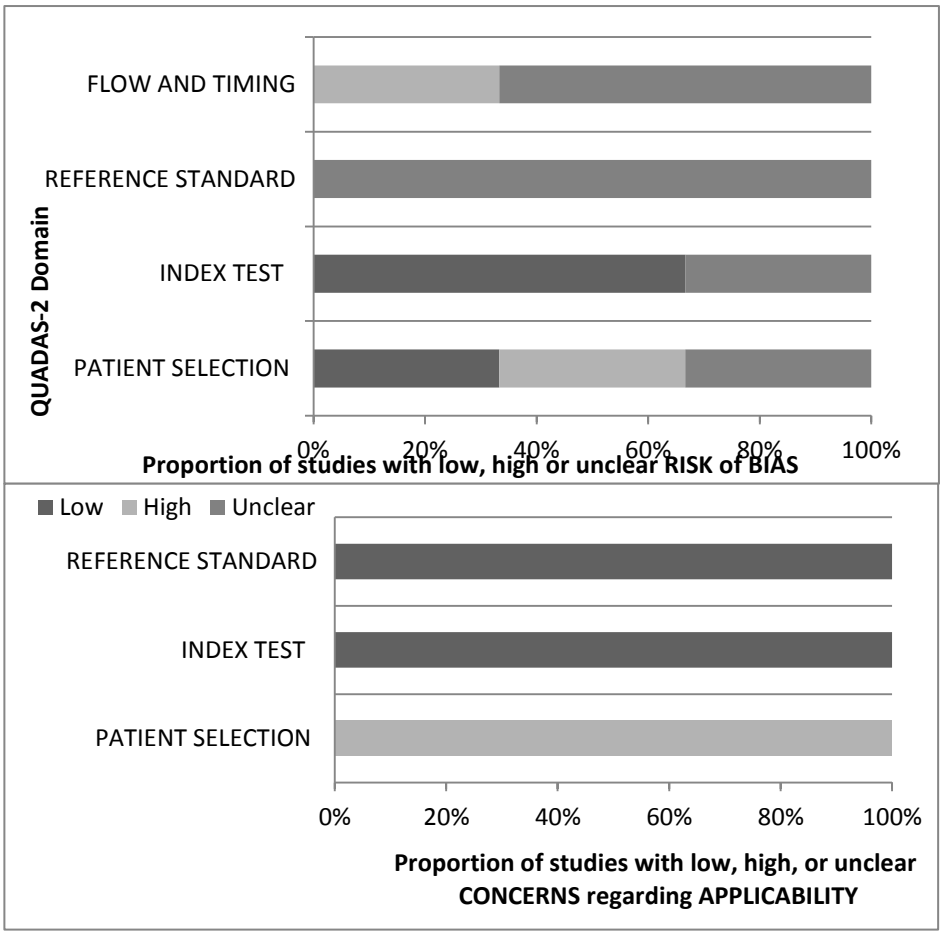
Figure 24. Study flow diagram



Study quality and results

Three studies reporting diagnostic accuracy were assessed for risk of bias and applicability with the QUADAS-2 tool. All studies included patients who were not relevant to review question (e.g. patients with suspicion of upper tract tumours who did not have new or recurrent bladder cancer). It was only clear in one study (Jinzaki *et al.*, 2011) that inappropriate exclusions were avoided. In all studies, patients received a different reference standard (surgery or follow-up imaging) and the interval between the index test and the reference standard was unclear. In Metser *et al.* (2012) the numbers used to calculate sensitivity and specificity do not correlate with the number of patients or upper tract lesions reported, and caution is warranted when interpreting data from the study. A summary of the QUADAS-2 quality assessment is provided in Figure 25.

Figure 25. QUADAS-2 quality assessment



Evidence statements

Sensitivity and specificity for presence of tumour in upper tract

Three studies reported the diagnostic accuracy of multi-detector CT urography for the detection of tumour in the upper tract; with sensitivity ranging from 88% to 100% and specificity ranging from 91% to 95% (see Table 28). One study also reported the diagnostic accuracy of excretory urography for the detection of tumour in the upper tract, with sensitivity of 80% and specificity of 81% (Jinzaki et al., 2011). This study reported that sensitivity and specificity of CT urography was significantly greater than excretory urography.

The proportion of upper tract tumours detected by intravenous urography/CT urography is shown in Table 29. Three low quality studies (1340 patients) reported the incidence of upper urothelial tract tumours at diagnosis of bladder cancer, which ranged from 0.3% to 1.7% across studies. Herranz-Amo et al. (1999) reported that intravenous urography (IVU) detected six out of the nine (67%) upper tract tumours. Three low quality studies reported the incidence of upper tract tumours during follow-up of bladder cancer. In Hession et al. (1999) 3.4% of patients developed an upper tract tumour, all of which were detected on IVU but there were also two false positive cases. Miyake et al. (2006) reported that 20 (4.6%) patients developed an upper tract tumour during follow-up, two of which were detected by routine IVU and 18 of which presented with symptoms that initiated extra IVU. Meissner et al. (2007) reported on 322 patients undergoing follow-up after radical cystectomy. 15 (4.7%) developed an upper tract tumour, eight of which were detected by routine IVU. One study (Shinagare et al., 2013) reported on 105 patients undergoing CT urogram for follow-up after radical cystectomy. Three (2.9%) patients developed an upper tract tumour.

No evidence was identified for the other outcomes specified in the PICO (change in management, overall survival, progression-free survival, and morbidity associated with the procedure).

Table 28. Patient-level sensitivity and specificity for presence of tumour in upper urinary tract

Study	Population	Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Jinzaki 2011	104 with asymptomatic haematuria. 46% with new or prior bladder cancer.	MDCT urography	94	95	93	95
		Excretory urography	80	81	77	84
Xu 2010	168 undergoing routine surveillance for urothelial tumour. 53% prior bladder cancer.	MDCT urography	100	91	62	100
Metser 2012	77 at risk for urothelial malignancy. 31% newly diagnosed bladder cancer, 18% after resection of bladder tumour	MDCT urography (urothelial phase and excretory phase)	88	91	71	97

Table 29. Incidence of upper urothelial tract tumours and proportion detected by intravenous urography/CT urography

Study	Population	Test	Incidence of UUTT	Detection by IVU
Bajaj 2007	233 with newly diagnosed bladder cancer and IVU at initial presentation	IVU at diagnosis	1.7% (4/233)	22 patients had equivocal IVU findings. All had normal further imaging or follow-up imaging
Herranz-Amo 1999	793 with primary bladder cancer	IVU prior to TURBT	1.1% (9/973)	IVU detected 67% (6/9)
Goessl 1997	314 with newly diagnosed bladder cancer	IVU at diagnosis	0.3% (1/314)	6 cases suspicious on IVU which was normal on retrograde pyelography or ureterorenoscopy in 5 cases
Hession 1999	174 undergoing routine follow-up for bladder cancer	IVU follow-up	3.4% (6/174)	8 cases suspicious on IVU, 2 of which false positives on retrograde pyelography
Miyake 2006	413 undergoing follow-up for bladder cancer	IVU follow-up	4.8% (20/413)	2 diagnosed by routine IVU. 18 presented with symptoms which resulted in extra IVU
Meissner 2007	322 after radical cystectomy and ileal orthotopic bladder substitution	IVU follow-up	4.7% (15/322)	8 diagnosed by routine IVU.
Shinagare 2013	105 after radical cystectomy	CTU follow-up	2.9% (3/105)	Findings suggestive of UUTT in 11 (10.5%) patients. 7 false positive, 3 true positive.

References to included studies

Bajaj, A, Sokhi, H, and Rajesh, A. Intravenous urography for diagnosing synchronous upper-tract tumours in patients with newly diagnosed bladder carcinoma can be restricted to patients with high-risk superficial disease. Clinical Radiology 2007; 62(9): 854-857.

Goessl, C. Is routine excretory urography necessary at first diagnosis of bladder cancer? Journal of Urology 1997; 157(2): 480-481.

Herranz-Amo, F et al. Need for intravenous urography in patients with primary transitional carcinoma of the bladder? European Urology 1999; 36(3): 221-224.

Hession, P et al. Intravenous urography in urinary tract surveillance in carcinoma of the bladder. Clinical Radiology 1999; 54(7): 465-467.

Jinzaki, M et al. Comparison of CT urography and excretory urography in the detection and localization of urothelial carcinoma of the upper urinary tract. AJR 2011; American Journal of Roentgenology. 196(5): 1102-1109.

Meissner, C et al. The efficiency of excretory urography to detect upper urinary tract tumors after cystectomy for urothelial cancer. Journal of Urology 2007; 178(6): 2287-2290.

Metser, U. Detection of urothelial tumors: Comparison of urothelial phase with excretory phase CT urography - A prospective study. Radiology 2012; 264(1): 110-118.

Miyake, H et al. Limited significance of routine excretory urography in the follow-up of patients with superficial bladder cancer after transurethral resection. BJU International 2006; 97(4): 720-723.

Shinagare, AB, Sadow, CA, and Silverman, SG. Surveillance of patients with bladder cancer following cystectomy: yield of CT urography. Abdominal Imaging 2013; 38(6): 1415-1421.

Xu, AD et al. Significance of upper urinary tract urothelial thickening and filling defect seen on MDCT urography in patients with a history of urothelial neoplasms. AJR 2010; American Journal of Roentgenology. 195(4): 959-965.

References to excluded studies (with reasons for exclusion)

Dalbagni, G. Can excretory urography detect upper urinary tract tumors after radical cystectomy for urothelial cancer? Nature Clinical Practice Urology 2008; 5(6): 302-303.

Reason: comment on Meissner

Milestone, B et al. Staging of Ureteral Transitional Cell-Carcinoma by Ct and Mri. Urology 1990; 36(4): 346-349

Reason: not relevant to PICO/ not relevant to current practice

Fritz, GA et al. Multiphasic multidetector-row CT (MDCT) in detection and staging of transitional cell carcinomas of the upper urinary tract. European Radiology 2006; 16(6): 1244-1252.

Reason: outcomes not relevant – no sensitivity and specificity for detection

Cowan, NC et al. Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumour. BJU International 2007; 99(6): 1363-1370.

Reason: population not relevant to PICO

Razavi, SA et al. Comparative effectiveness of imaging modalities for the diagnosis of upper and lower urinary tract malignancy: a critically appraised topic. Academic Radiology 2012; 19(9): 1134-1140.

Reason: non-systematic review

Mueller-Lisse, UG et al. Multidetector-row computed tomography (MDCT) in patients with a history of previous urothelial cancer or painless macroscopic haematuria. European Radiology 2007; 17(11): 2794-2803.

Reason: population and outcomes not relevant to PICO

Sadow, CA et al. Positive predictive value of CT urography in the evaluation of upper tract urothelial cancer. AJR 2010; American Journal of Roentgenology. 195(5): W337-W343.

Reason: population not relevant to PICO

Hwang, EC et al. Accuracy and factors affecting the outcome of multi-detector computerized tomography urography for bladder tumors in the clinical setting. Korean Journal of Urology 2011; 52(1): 13-18.

Reason: outcomes not relevant to PICO (detection of bladder tumours)

McCoy, JG et al. Computerized tomography for detection and staging of localized and pathologically defined upper tract urothelial tumors. Journal of Urology 1991; 146(6): 1500-1503.

Reason: population not relevant to PICO

Chlapoutakis, K et al. Performance of computed tomographic urography in diagnosis of upper urinary tract urothelial carcinoma, in patients presenting with hematuria: systematic review and meta-analysis (Structured abstract). European.Journal of Radiology 2010; 73(2): 334-338.

Reason: population not relevant to PICO

Planz, B et al. Computed tomography for detection and staging of transitional cell carcinoma of the upper urinary tract. European Urology 1995; 27(2): 146-150.

Reason: population not relevant to PICO

Sternberg, IA et al. Upper tract imaging surveillance is not effective in diagnosing upper tract recurrence in patients followed for nonmuscle invasive bladder cancer. Journal of Urology 2013; 190(4): 1187-1191.

Reason: method of imaging not reported

Wu, G-Y. Comparison of computed tomographic urography, magnetic resonance urography and the combination of diffusion weighted imaging in diagnosis of upper urinary tract cancer. European Journal of Radiology 2014; 83(6): 893-899.

Reason: population not relevant to PICO (not bladder cancer)

Evidence tables

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
Bajaj 2007 UK	Retrospective review – audit of existing practice	Low – retrospective observational study	Out of 330 consecutive patients with TCC bladder over 2 yrs (2003-2004), 233 had IVU at initial presentation	Mean age 68 years (range 42-88) Mean time from diagnosis of primary tumour to IVU =40 days.	IVU for the presence of synchronous upper-tract tumours	UT TCC confirmed on histology in all 4 patients with positive IVU.	Incidence of upper tract tumours = 4/233 (1.7%). All 4 had Ta bladder cancer without CIS. 2 had multifocal disease. 22 patients had equivocal finding on IVU. 9 of these 22 had further imaging (CT or further IVU) which was normal. Routine follow-up of remaining patients failed to reveal any progression to clinically significant disease. 2 patients who had an IVU developed UT tumour at 15 and 17 mo follow-up. 1 patient who did not have IVU developed UT tumour at 34 mo.		97 patients did not adhere to local protocol and did not undergo IVU. Sensitivity and specificity of imaging not reported
Herranz-Amo 1999 Spain	Retrospective review	Low – retrospective observational study	793 patients with confirmed primary bladder tumour 1986-1996 with IVU prior to TURBT	Mean age 66.4 ±11.2 (range 16-91) 88% male, 12% female 10% G1, 45% G2, 45% G3. 81% solitary tumour. 72% NMIBC, 28% MIBC	IVU for the presence of synchronous upper-tract urothelial tumours (UTUT)	Not reported how suspicious IVU findings were confirmed.	Incidence of upper tract tumours = 9/793 (1.1%). Confirmed in 6 patients (other 2 were uric stones in renal pelvis, and 1 suspected UTUT not confirmed by retrograde pyelography). In 3 patients suspected UT was confirmed at TUR – these 3 exhibited non-functioning kidneys at IVU and anterograde pyelography confirmed diagnosis. Therefore, IVU identified 66.6% of UTUTs 146 (18%) showed abnormality e.g. renal mass, obstructive uropathy. No difference in the incidence of UTUTs with regard to gender, histological grade, multiplicity, superficial or infiltrative.		Sensitivity and specificity of imaging not reported
Goessl 1997 Germany	Retrospective review	Low – retrospective observational study	314 consecutive patients with newly diagnosed bladder cancer 1988-1994	128 women, 186 men. Mean age 73 (range 31-96) 33% MIBC. All but 2 were TCC.	Routine excretory urography (IVP) performed with non-ionic contrast medium iopamidol. Plain film of the abdomen followed by further images 5, 15, and 30 mins after infusion. When delayed excretion of the contrast medium was observed images were repeated up to 24h after infusion. IVP images re-evaluated by 2 senior urologists. Urological and non-	N/a	IVP suspicious for ureteral or renal pelvic tumour in 6 patients (1.9%). This suspicion was eradicated with retrograde pyelography or ureterorenoscopy in 5 cases. Only 1 silent upper urinary tract tumour was detected with IVP resulting in nephroureterectomy. Urinary obstruction could equally be seen with IVP and ultrasonography.		Sensitivity and specificity of imaging not reported

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
					urological pathologies were analysed and result compared with the written former urographic findings from the charts. Ultrasound of kidneys and bladder also performed (original images not available in all cases)				
Hession 1999 UK	Retrospective cohort study	Low quality – retrospective study	174 consecutive patients with bladder cancer (140 NMIBC) undergoing routine follow-up	132 male, 42 female. Mean age 59 (range 20-84).	IVP at primary presentation, 12 months, and 24 month intervals thereafter. Median follow-up 8.3 y (range 1-30). Average number of IVUs per patient = 3.7	n/a	102 (58.6%) had normal IVU at presentation. Commonest abnormality on IVU was a bladder filling defect (61, 35.1%). No synchronous UTT were found. Of the 164 patients evaluated cystoscopically at 12mo, 83 (50.6%) had recurrent TCC of the bladder. 156 patients (95%) had normal IVU at this time. Upper tract filling defects were identified in 8 patients, 6 of which were proven TCC (2 FNs on retrograde pyelography), mean 78mo (range 12-132) post-presentation. 5/6 had solitary tumour at presentation. All of those who subsequently developed UTT had recurrent bladder tumour within 24 months. 4/6 UUT occurred at 72 months or later.		Sensitivity and specificity of imaging not reported. Paper also included in evidence review for topic K1.
Miyake 2006 Japan	Retrospective cohort study	Low quality - retrospective study, unclear if consecutive sample	413 newly diagnosed NMIBC 1986-2003.	326 male, 87 female. 265 were <70 years old. 52 received intravesical chemotherapy, 45 BCG therapy. Median follow-up 102 months	IVU before TUR but UUT washings were analysed at the time of or before initial TUR in patients who were diagnosed as positive by urinary cytological examination. Follow-up consisted of cystoscopy and cytology every 3mo for 2yrs after TUR, then every 6mo at 3-5yrs and then annually thereafter. IVU every 6mo until 3yrs after TUR and then annually until 5 yrs. At 5yrs the examinations were at the patients request	n/a	20/413 (4.8%) upper tract tumours were detected. The median (range) time from initial TUR to diagnosis of subsequent UUTCs was 33 (6-165) months. No differences between patients in age/gender/growth pattern/grade/stage/tumour size/CIS/chemo or BCG therapy. Patients with UUT recurrence had a higher incidence of multiple tumours at initial TUR than those with no recurrence. No independent predictors for UUT recurrence. Only 2 patients were diagnosed as having UUTC by routine IVU. The remaining 18 presented with symptoms which were an incentive to examine the UUT by extra IVU (macrohaematuria 10, intravesical recurrence 5, +ve urine cytology 5, abdominal pain 3, high fever 2)		Sensitivity and specificity of imaging not reported. Paper also included in evidence review for topic K1.

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
							After detecting some symptoms IVU failed to show findings suspicious of recurrent UUTCs in 10 of 18 patients and these 10 were diagnosed by other methods inc retrograde pyelography, CT and/or ureterorenoscopy.		
Jinzaki 2011 Japan	Retrospective review	Image review blinded, population not all relevant to PICO, not all patients received same reference standard, interval between ref standard and imaging varied between patients	104 consecutive patients with asymptomatic haematuria who had both CT urography and excretory urography before treatment 2002-2007. (of 128 patients, 24 were excluded due to lack of established final diagnosis)	85 male, 19 female. Mean age 66.9y (range 40-88) 56 referred for suspicion of UUT because of haematuria with no abnormality at cystoscopy (n=35), abnormal findings in UUT at sonography (n=15), positive cytology and no abnormality at cystoscopy (n=6). 48 (46%) referred due to new (n=43) or prior (n=5) bladder cancer diagnosis.	CT urography on 16- or 64-MDCT scanners using a 3-phase protocol. All administered 400-500ml of water orally 20mins before the exam. Unenhanced CT scans of abdomen and pelvis were obtained (5mm thick sections). Nephrographic phase images (5mm thick sections) were then obtained from the diaphragm through the kidneys beginning 100secs after a 30sec injection of iohexol at a dose of 2ml/kg. Excretory phase images of the abdomen and pelvis were obtained 8 mins after contrast injection (1.25mm thick images). Lesions considered suspicious for UUT included one or more filling defects, wall irregularity, or hydronephrosis.	Final diagnosis determined by surgery (n=46) or ureteroscopy with biopsy (n=3). Follow-up CT urography or excretory urography at 1 year or later used to confirm benign findings. Mean time between CTU and surgery 44 days (±27). Mean time between IVU and surgery 34 days (±23)	**CT urography** TP 43 TN 55 FP 3 FN 3 **Excretory urography** TP 37 TN 47 FP 11 FN 9 46/104 (44%) had final diagnosis of UUTUC. Of the 58 patients with no upper tract findings, 39 were diagnosed with bladder cancer.	**CT urography** Sens 94 Spec 95 PPV 93 NPV 95 **Excretory urography** Sens 80 Spec 81 PPV 77 NPV 84	Nephrographic phase images were not included in the evaluation. Per-patient analysis – CT urography significantly better than excretory urography
Xu 2010 USA	Retrospective review	150 patients without imaging or follow-up excluded, population not all relevant to PICO, unclear if image review was blind to other results, not all patients received same ref standard.	168 CT urography exams for 111 (out of 326 consecutive patients) patients undergoing routine surveillance for a history of urothelial tumour 2006-2009	78% male, 22% female. Median age 65.5 (range 32-90). History of bladder cancer (n=89), UT (n=8), bladder and UT (n=13), prostatic urethra (n=1)	CT urography using 64-MDCT scanner. Barium preparation used as an oral contrast medium. 1st dose 90mins before examination, 2nd dose when patient was on CT table. IV 250ml normal saline was administered 15-40 mins before the exam. Split-bolus technique and consisted of 3 phases: noncontrast, portal venous, and 10min combined nephrographic/pyelographic phase. 10mg furosemide given IV before the first injection of contrast. Initial CT urography	Pathologic analysis on surgical resection or clear visualisation of tumour on ureteroscopy. A follow-up CT urogram used as confirmatory in false positive and true negative exams.	**CT urography (per examination analysis)** TP 21 TN 134 FP 13 FN 0 Histologically proven UTTs identified in 21 patients	**CT urography (per examination analysis)** Sens 100 Spec 91 PPV 62 NPV 100	Excluded 158 patients with stents and those with examinations without any imaging or pathologic follow-up (n=150).

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
					reports were reviewed by one of the authors for upper tract lesions.				
Metser 2012 Canada	Prospective observational study	Unclear if consecutive sample used, population not all relevant to PICO, image review blinded, unclear if ref standard was interpreted without knowledge of index test, reference standard and interval between imaging and ref standard unclear, unclear how sensitivity and specificity were calculated – numbers do not match reported number of patients/ lesions.	77 sent for staging of proven bladder cancer or upper tract tumour, those with suspicious tumour before histologic proof, and patients with positive cytology and negative cystoscopy	57 male, 20 female. Median age 69 (range 28-88) Staging newly diagnosed UT (n=4) or bladder (n=25) tumours; assessment of upper tract after resection of bladder tumour (n=14); suspicion of urothelial malignancy at other imaging not confirmed with histology or cytology (n=4 UT, n=6 bladder; positive cytology and negative cystoscopy (n=27)	CT urography: 64 row MDCT scanner. Oral hydration and iv diuretic were administered prior to contrast material injection. All drank 750ml of water 30-45mins before scan. 100-300ml iodixanol 3ml/sec, images acquired at 60 seconds (urothelial phase) and 5 minutes (excretory phase) by using the same scanning parameters. Images displayed in the axial (3mm section thickness, 1.5mm interval), coronal (3mm, contiguous) and sagittal (3mm, contiguous) planes. Presence or absence of lesion was recorded using a standardised data collecting sheet by two trained abdominal radiologists.	Any lesion identified was further evaluated. Only urothelial tumours that were confirmed histologically were considered positive. Lesions that were not confirmed as malignant at histologic, cytologic, cystoscopic, or ureteroscopic examinations were considered false positive.	**Urothelial phase CT urography (lesion level analysis)** TP 38 TN 121 FP 5 FN 8 **Excretory phase CT urography (lesion level analysis)** TP 32 TN 116 FP 10 FN 14 **Combined UP and EP phase CT urography (lesion level analysis)** TP 39 TN 114 FP 12 FN 7 **Combined UP and EP phase CT urography (patient level analysis)** TP 30 TN 114 FP 12 FN 4	**Urothelial phase CT urography (lesion level analysis)** Sens 83 Spec 96 PPV 88 NPV 94 **Excretory phase CT urography (lesion level analysis)** Sens 70 Spec 92 PPV 76 NPV 89 **Combined UP and EP phase CT urography (lesion level analysis)** Sens 85 Spec 91 PPV 77 NPV 94 **Combined UP and EP phase CT urography (patient level analysis)** Sens 88 Spec 91 PPV 71 NPV 97	UP was more sensitive and accurate than EP although this reached statistical significance only for lesion-based analysis.
Meissner 2007 Switzerland	Prospective observational study	Low – observational study	322 who underwent RC and ileal orthotopic neobladder	Mean age at RC 65y (range 36-83). Male to female ratio 14:1. Median follow-up 49	Excretory urography (IVP) assessed upper tract 1, 2, 3, 5, 7 and 10 years after cystectomy.	n/a	**UUTT rate:** 15/322 (4.7%) median of 31 mo (range 12-72) after RC. 8/12 (53%) UUTTs were diagnosed by routine IVP. The other 7 lesions were detected by further examinations initiated because of		105 patients with follow-up of less than 12mo were excluded.

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
			substitution for bladder TCC 1985-2006 and had regular follow-up.	months (range 12-220)			haematuria or flank pain. Overall 1064 IVPs were performed and 8 UUTs were detected (0.75%)		Sensitivity and specificity of imaging not reported.
Shinagare 2013 USA	Retrospective cohort study 200-2011	Low-observational study	N=105 patients having CT urogram during follow-up after RC for bladder cancer	79 male, 26 female. Mean age 65 (range 43-85)y Median time between RC and CTU 39 months (0-229)	CTU using 4-, 16- or 64-detector CT scanners. Single bolus 3-phase protocol used (unenhanced scan of abdomen and pelvis, nephrographic scan phase of kidneys after i.v. injection, excretory phase scan of abdomen and pelvis 15min after contrast medium injection.	n/a	225 CTUs were performed in 105 patients. **Findings related to surgery:** 60/105 (57%). Of 60 patients with findings relating to complications from surgery, 5 (8.3%) required surgery. **Locoregional or distant recurrence of bladder cancer:** 21 (20%) Visceral mets 16 (15.2%), lymph node metastases 13 (12.4%), pelvic recurrence 1 (1%). Of 21 patients, 7 had coexisting nodal and distant mets and one had local recurrence with nodal and distant mets. **UUT recurrence:** 3/105 (2.9%) Findings suggestive of UTT were seen in 11 (10.5%). Of these, 7 were false positive, 3 were true positive, and one was lost to follow-up. UUT developed after a median of 43 months (range 16-73) months from surgery.		Unclear how patients were selected – potential selection bias. Unclear if CTU was performed routinely.

2.4.3 Detecting thoracic malignancy

Review question: (CT versus chest X-ray or PET-CT for thoracic malignancy) In patients with high risk NMIBC or MIBC is chest CT, chest PET-CT or chest X-ray the most effective method for the detection of thoracic malignancy and can these tests be omitted in patients with NMIBC?

Rationale

Chest x-ray is also a cheap and universally available imaging technique, it is useful in the diagnosis of lung metastases and of primary lung cancer but is of lower sensitivity than chest CT, it may have a role in the work up of patients with newly diagnosed bladder cancer as these patients are often elderly and smokers and have an increased risk of lung cancer.

Question in PICO format

Populations	Test	Comparators	Outcomes
High risk NMIBC MIBC	Chest CT	Chest X-Ray PET-CT NO imaging (in high risk NMIBC population only	• Sensitivity and specificity * for thoracic malignancy • Change in management • Overall survival • Progression free survival • Morbidity associated with the test procedure

METHODS

Information sources

A literature search was also performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

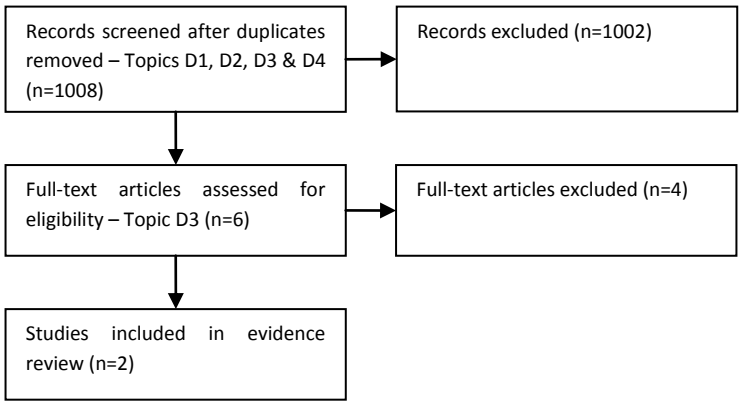
Data synthesis

Two studies were identified for this review question. A meta-analysis was not possible.

RESULTS

Result of the literature searches

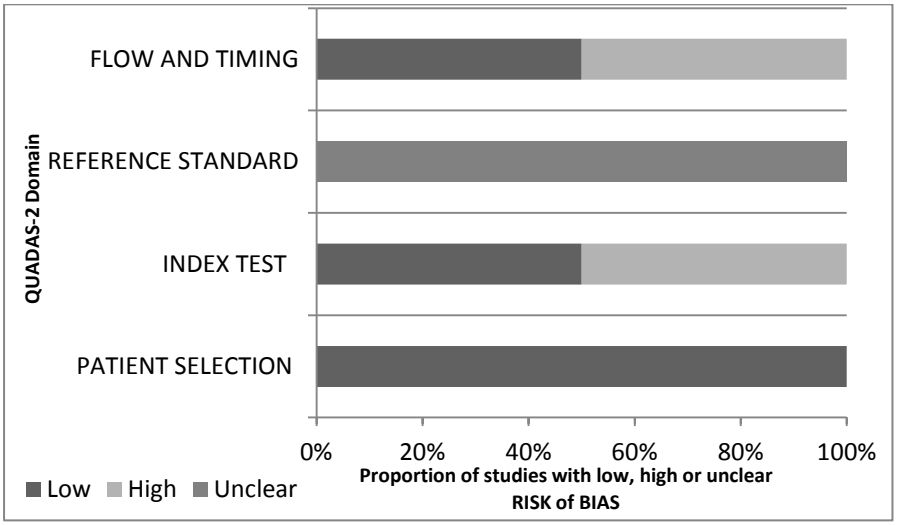
Figure 26. Study flow diagram



Study quality and results

Two studies were included in the evidence review (Lodde *et al.*, 2010; Yang *et al.*, 2012a). Risk of bias and applicability were assessed using the QUADAS-2 tool. Both studies were applicable to the review question. Both studies had a low risk of bias for patient selection, although in Lodde *et al.* (2010) it was unclear if a consecutive or random sample of patients was used. Studies were judged to have a high or unclear risk of index test bias because the index test was reported with knowledge of clinical history or the results of other imaging tests. In both studies it was unclear if the reference standard was interpreted without knowledge of the index test. In Yang *et al.* (2012a) not all patients received the same reference standard. Lodde *et al.* (2010) did not report the sensitivity and specificity of CT and PET-CT for detecting thoracic malignancies.

Figure 27: Results of QUADAS-2 risk of bias assessment



Evidence statements

Moderate quality evidence from two studies which investigated whole body FDG PET-CT scans for the staging of bladder cancer was identified. Lodde *et al.* (2010) included 44 patients with MIBC before radical cystectomy, 19 patients under follow-up after cystectomy, and seven after systemic chemotherapy. For the detection of extrapelvic metastases, 36 patients who had six months or more of imaging follow-up were included. In five patients, standard CT detected lung nodules that

did not accumulate FDG, and in one retroperitoneal node, also negative at PET. None of these patients had progressed on subsequent follow-up imaging. Yang *et al.* (2012a) included 60 bladder cancer patients undergoing whole body PET-CT for routine follow-up, for the detection of suspected metastasis, or for monitoring treatments. 15 lung lesions were indentified. The sensitivity and specificity of PET-CT for detecting lung metastases was 85.7% and 100%, respectively. Two lung lesions were considered to be false negative, as they were validated to be malignant during follow-up, but with no abnormal FDG uptake. Both lesions were smaller than 1.5cm, so the diagnosis of CT was also ambiguous. PET-CT correctly changed the management in 15 (25%) patients.

No evidence was identified for chest x-ray, or for the outcomes of overall survival, progression-free survival and morbidity associated with the test procedure.

References to included studies

Yang, Z et al. Clinical value of whole body fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in the detection of metastatic bladder cancer. International Journal of Urology 2012; 19(7): 639-644.

Lodde, M et al. Evaluation of fluorodeoxyglucose positron-emission tomography with computed tomography for staging of urothelial carcinoma. BJU International 2010; 106(5): 658-663.

References to excluded studies (with reasons for exclusion)

Gedik, GK. Evaluation of FDG uptake in pulmonary hila with FDG PET/CT and contrast-enhanced CT in patients with thoracic and non-thoracic tumors. Annals of Nuclear Medicine 2010; 24(8): 593-599.

Reason: population not relevant to PICO

Kang, MC et al. Accuracy of 16-channel multi-detector row chest computed tomography with thin sections in the detection of metastatic pulmonary nodules. European Journal of Cardio-Thoracic Surgery 2008; 33(3): 473-479.

Reason: population not relevant to PICO

Sutton, S, Cohen, AM, and Resnick, MI. Value of chest computed tomography in genitourinary malignancies. Urology 1983; 22(6): 667-668.

Reason: not relevant to current practice

Lipman, RA. Whole-lung tomography in urologic malignancy. Urology 1989; 34(4): 227-229.

Reason: intervention not in PICO/ not relevant to current practice

Evidence tables

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
Lodde 2010 Canada	Observational study – appears prospective	Low risk of bias, unclear if image review was blinded, not all patients had CT + PET/CT, unclear if consecutive or random sample of patients was used.	44 MIBC scheduled to have RC with no neoadjuvant chemo, 19 under follow-up after RC, 7 re-staging after chemo for locally advanced and mets BC For extrapelvic mets, 36 patients who had ≥6mo imaging follow-up were included	13 female, 57 male. Mean age 67 (range 49-86). 39 primary UC, 4 primary epidermoid, 1 neuroendocrine, 12 associated primary prostate cancer. All had bone scintigraphy.	Whole body FDG-PET/CT: using PET/CT integrated system. Images acquired 75min after injection with 333-407 MBq of FDG. CT with oral contrast material but without i.v. contrast medium. Images reviewed with fusion of CT and PET images. No catheterization required. Standard thoracic and adomino-pelvic CT scan and bone scintigraphy. Any LN >1cm considered positive. Some cases of <1cm but multiple were considered positive. SUVmax was determined. Lesions with FDG accumulation on a confirmed anatomical structure were considered positive.	Histopathology from bladder and PLN obtained at cystoprostatectomy or anterior pelvic exoneration. All but 2 patients had extended lymphadenectomy. Mean time CT and surgery=25.4 days, between PET and surgery =30 days	Suspicious extrapelvic areas on FDG-PET/CT in 20 patients including 13 suspicious lung images. 2 patients had rapid progression of lung lesions and died from UC. 2 lesions were confirmed primary lung cancer. Another with lung lesions also had pathological thyroid FDG uptake, confirmed as thyroid carcinoma at biopsy. Of 4 patients with FDG PET/CT lung images, one died from massive pulmonary embolism, the other 3 did not progress at a mean follow-up of 7.1 (7-10) months, and images in the lung were attributed in two cases to an inflammatory disease, and in one nature of lesion remains unknown. In 5 patients, standard CT detected lung nodules that did not accumulate FDG, and in one a retroperitoneal node, also negative at PET. None have progressed on subsequent follow-up imaging.		33 had CT and PET/CT, 11 had only PET/CT. Study also included in topic D1.
Yang 2012 China	Retrospective study	Moderate risk of bias, consecutive sample used, index test was interpreted with knowledge of clinical history and other imaging results, not all patients received same reference standard (biopsy or further imaging).	60 consecutive patients with a history of bladder cancer referred 2006-2010 for whole body FDG PET-CT scans.	Male 77%, female 23%. Median age 60.5 (range 32-96) 22 N0, 27 N1, 11 N2. 16 had cystectomy, 44 had chemo, radiotherapy or chemo-radiotherapy. 25 routine follow-up scan, 22 detection of suspected mets, 13 monitoring treatments.	Whole body FDG PET-CT using Explora FDG_4 module. All required to fast for at least 6h. Scanning 1h after administration of tracer (7.4MBq/kg). Images obtained on Siemens biograph 16HR PET-CT scanner. Abnormal FDG uptake was defined as radiotracer accumulation that was thought to be outside of normal anatomical structures. SUVmax for each lesion was calculated. Reviewing physicians were aware of clinical history and other imaging.	All suspicious PET-CT lesions were assessed further using biopsies or subsequent imaging. 24 verified by biopsy, 100 validated by serial imaging or other clinical examinations for at least 6 months (98 CT, 12 MRI)	Suspicious lung lesions (n=15, 11.5%) TP 12 TN 1 FP 0 FN 2 PET/CT correctly changed management in 15 patients (25%)	Sens 85.7 Spec 100 PPV 100 NPV 33	Organ based analysis of sensitivity and specificity. Study also included in topic D4

2.4.4 Detecting bone metastases

Review question: (CT versus MRI, PET-CT and bone scintagraphy for bone metastases) In patients with high risk NMIBC or MIBC is CT, MRI or bone scintagraphy the most effective method for the detection of bone metastases and can these tests be omitted in patients with NMIBC?

Rationale

Bone metastases generally occur in the context of more advanced disease and are often detected on CT or MRI, bone scan is potentially more sensitive but has limited specificity and is not used as part of routine staging in most centres.

Question in PICO format

Populations	Test	Comparators	Outcomes
High risk NMIBC MIBC	CT	MRI Bone scintigraphy No imaging (in high risk NMIBC population only	• Sensitivity and specificity * for Bone metastases • Change in management • Overall survival • Progression free survival • Morbidity associated with the test procedure

*Compared to reference standard of histopathology of surgical specimens or clinical/radiological follow up when there is no surgery.

METHODS

Information sources

A literature search was also performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

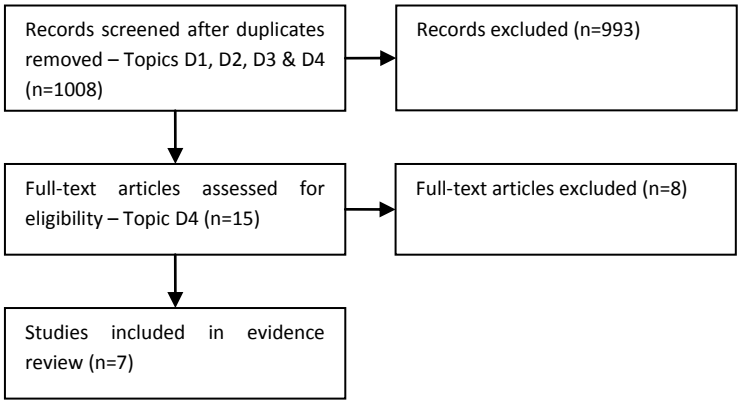
Data synthesis

A narrative summary of the evidence is reported.

RESULTS

Result of the literature searches

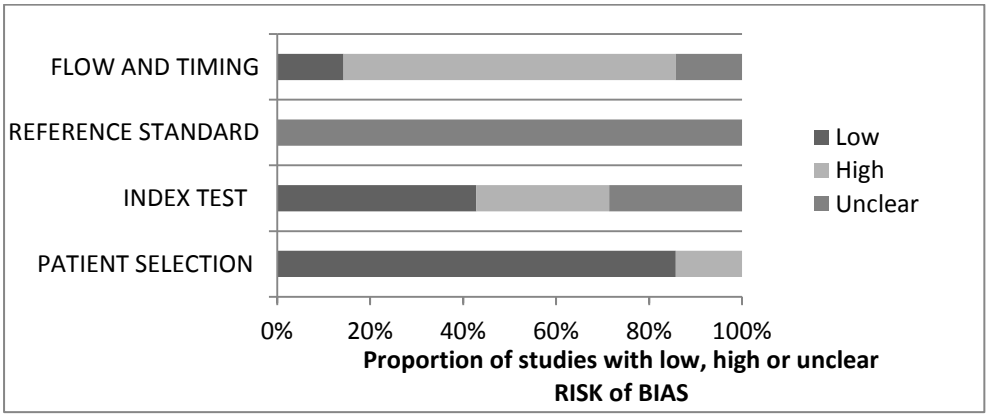
Figure 28. Study flow diagram



Study quality and results

Seven studies were included in evidence review (Chakraborty *et al.*, 2013; Balliu *et al.*, 2010; Braendengen *et al.*, 1996; Brismar & Gustafson, 1988; Davey *et al.*, 1985; Yang *et al.*, 2012b; Lodde *et al.*, 2010). Risk of bias and applicability were assessed using the QUADAS-2 tool. With regards to applicability, one study (Balliu *et al.*, 2010) included patients with cancers other than bladder. In the study by Brismar & Gustafson (1988) the reference standard was poorly reported so it was unclear whether it was applicable. Risk of bias regarding the reference standard was unclear in all studies as it was not reported whether the reference standard was interpreted without knowledge of the bone scintigraphy results. Flow and timing bias was high in a majority of studies as not all patients received the same reference standard (follow-up blood tests or additional imaging) and the interval between the index test and follow-up was not reported.

Figure 29. Risk of bias of included studies



Narrative summary of evidence

Seven studies were included in the evidence review. One study (Balliu, 2010) compared whole body MRI with bone scintigraphy for the detection of bone metastases in patients with primary malignant solid tumours (breast and lung, n=19) or other malignant tumours with clinical signs and symptoms suggestive of bone metastases (n=19). Metastases were present in 18 (47%) patients. Diagnostic accuracy was higher for whole-body MRI than for bone scintigraphy. The sensitivity and specificity was 94% and 90% for MRI, and 72% and 75% for bone scintigraphy respectively. There were 5 false negatives and 5 false positive results with bone scintigraphy, and 1 false negative and 2 false positive results with MRI. In another comparative study (Chakraborty, 2013), 48 patients with locoregional or metastatic bladder cancer and with a high likelihood of bone metastases underwent ^{99m}Tc-MDP and single-photon emission computed tomography (SPECT/CT) bone scan followed by ^{18}F-flouride

PET/CT within 48 hours. The sensitivity and specificity of ^{99m}Tc-MDP SPECT/CT was 88% and 74%, respectively. ^{99m}Tc-MDP SPECT/CT correctly detected 15 out of 48 patients as having metastases and 23 patients without metastases. 2 patients showed false-negative findings and 8 were detected as false-positives. With ^{99m}Tc-MDP planar bone scan 11 patients had false-positive and 3 patients had false-negative findings. The sensitivity and specificity for ^{99m}Tc-MDP planar bone scan was 82% and 65%, respectively. The sensitivity and specificity of ^{18}F-fluoride PET/CT was 100% and 87%, respectively. 21 patients showed abnormal tracer uptake on ^{18}F-fluoride PET/CT, of which 17 (35%) were diagnosed with bone metastases based on definitive biopsy and imaging follow-up. Management was changed in these 17 patients to systemic therapy with chemotherapy and bisphosphonate therapy. In 2 patients, early malignant bony involvement was identified by ^{18}F-fluoride PET/CT but missed by planar bone scan and SPECT/CT.

Two studies assessed the clinical value of whole body FDG PET-CT in bladder cancer patients. One study (Lodde, 2010) reported that 36 patients bone scintigraphy results were available to be compared with FDG PET-CT. Both techniques detected the 3 (8%) patients with bone metastasis. In one case, additional pelvic and vertebral bone metastases were detected by FDG PET-CT only. In one study (Yang, 2012) of 60 patients, 134 suspicious lesions were identified from whole body FDG PET-CT. 7% (n=9) of these were bone lesions, which were all considered to be true positives. There were no false negative results.

Three studies reported the clinical value of routine bone scans in bladder cancer patients. In one study (Davey, 1985), 221 consecutive patients with invasive bladder cancer who were considered suitable for radical radiotherapy had routine bone scintigraphy. 14 (6%) patients had abnormal bone scintigrams considered to be consistent with bone metastases. 4 of these failed to develop clinical, radiographic, or biochemical evidence of skeletal disease during follow-up. 10 (5%) out of 207 patients with normal scintigrams at presentation developed bone metastases within 12-months of their original non-significant scan. Brismar (1988) reported a series of 71 patients who had bone scintigraphy for staging bladder cancer (67 of whom had no symptoms of bone metastases) and 26 patients previously treated for bladder cancer who presented with signs or symptoms suggestive of bone metastases. Out of the patients who had no signs or symptoms, 1 patient had findings suggestive of metastases, which was classified as a false positive at biopsy. In 7 out of 30 (23%) patients with signs or symptoms, metastases was identified by scintigram and later confirmed. In one patient with increased uptake the autopsy findings did not confirm the presence of bone metastases. One study (Braendengen 1996) reported that 35 out of 91 patients who had a pre-cystectomy bone scan had suspicion of metastases. 21 of these patients had a radiograph which was considered normal or due to degenerative changes. It is not clear how many patients were detected as having bone metastases from the scintigraphy alone or if the scintigraphy alone changed treatment.

Evidence statements

Two studies reported that the sensitivity and specificity of MRI and PET-CT were higher for the detection of bone metastases than bone scintigraphy. Indirect evidence was identified from five studies which reported the clinical value of bone scans in bladder cancer patients. These studies included patients undergoing routine bone scintigraphy for staging bladder cancer or because of a suspicion of bone metastases. The prevalence of bone metastases varied across studies from 6% to 23%. No evidence was identified for patients with non-muscle invasive bladder cancer. No

evidence was identified for the outcomes of overall survival, progression-free survival or morbidity associated with procedure.

References to included studies

Balliu E., B. Comparative study of whole-body MRI and bone scintigraphy for the detection of bone metastases. *Clinical Radiology* 2010; 65(12): 989-996.

Braendengen, M, Winderen, M, and Fossa, SD. Clinical significance of routine pre-cystectomy bone scans in patients with muscle-invasive bladder cancer. *British Journal of Urology* 1996; 77(1): 36-40.

Brismar, J and Gustafson, T. Bone scintigraphy in staging of bladder carcinoma. *Acta Radiologica* 1988; 29(2): 251-252.

Chakraborty, D et al. Comparison of 18F fluoride PET/CT and 99mTc-MDP bone scan in the detection of skeletal metastases in urinary bladder carcinoma. *Clinical Nuclear Medicine* 2013; 38(8): 616-621.

Davey, P et al. Bladder cancer: the value of routine bone scintigraphy. *Clinical Radiology* 1985; 36(1): 77-79.

Lodde, M et al. Evaluation of fluorodeoxyglucose positron-emission tomography with computed tomography for staging of urothelial carcinoma. *BJU International* 2010; 106(5): 658-663.

Yang, Z et al. Clinical value of whole body fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in the detection of metastatic bladder cancer. *International Journal of Urology* 2012; 19(7): 639-644.

References to excluded studies (with reasons for exclusion)

Ghanem, N et al. Comparative diagnostic value and therapeutic relevance of magnetic resonance imaging and bone marrow scintigraphy in patients with metastatic solid tumors of the axial skeleton. European Journal of Radiology 2002; 43(3): 256-261.

Reason: population not relevant to PICO

Gosfield, E, Alavi, A, and Kneeland, B. Comparison of Radionuclide Bone Scans and Magnetic-Resonance-Imaging in Detecting Spinal Metastases. Journal of Nuclear Medicine 1993; 34(12): 2191-2198.

Reason: population not relevant to PICO

Rajarubendra, N, Bolton, D, and Lawrentschuk, N. Diagnosis of Bone Metastases in Urological Malignancies-An Update. Urology 2010; 76(4): 782-790.

Reason: expert review

Reske, S et al. Bone marrow immunoscintigraphy compared with conventional bone scintigraphy for the detection of bone metastases. Acta Oncologica 1993; 32(7-8): 753-761.

Reason: population not relevant to PICO

Simms, MS et al. 99mTechnetium-C595 radioimmunoscintigraphy: a potential staging tool for bladder cancer. BJU International 2001; 88(7): 686-691.

Reason: outcomes not relevant to PICO

Talbot, J-N. Diagnosis of bone metastasis: Recent comparative studies of imaging modalities. Quarterly Journal of Nuclear Medicine and Molecular Imaging 2011; 55(4): 374-410.

Reason: non-systematic review

Urnes, T et al. The Value of Skeletal Scintigraphy in Detection of Metastic Bladder-Cancer Verified by Bone-Biopsy. Scandinavian Journal of Urology and Nephrology 1981; 93-96.

Reason: intervention not relevant to PICO

Zoeller, G et al. Bone marrow immunoscintigraphy versus conventional bone scintigraphy in the diagnosis of skeletal metastases in urogenital malignancies. European urology 1994; 26(2): 141-144.

Reason: outcomes not relevant to PICO

Evidence tables

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
Lodde 2010 Canada	Observational study – appears prospective	Low risk of bias, unclear if image review was blinded, not all patients had CT + PET/CT, unclear if consecutive or random sample of patients was used.	44 MIBC scheduled to have RC with no neoadjuvant chemo, 19 under follow-up after RC, 7 re-staging after chemo for locally advanced and mets BC For extrapelvic mets, 36 patients who had ≥6mo imaging follow-up were included	13 female, 57 male. Mean age 67 (range 49-86). 39 primary UC, 4 primary epidermoid, 1 neuroendocrine, 12 associated primary prostate cancer. All had bone scintigraphy.	Whole body FDG-PET/CT: using PET/CT integrated system. Images acquired 75min after injection with 333-407 MBq of FDG. CT with oral contrast material but without i.v. contrast medium. Images reviewed with fusion of CT and PET images. No catheterization required. Standard thoracic and adomino-pelvic CT scan and bone scintigraphy. Any LN >1cm considered positive. Some cases of <1cm but multiple were considered positive. SUVmax was determined. Lesions with FDG accumulation on a confirmed anatomical structure were considered positive.	Histopathology from bladder and PLN obtained at cystoprostatectomy or anterior pelvic exoneration. All but 2 patients had extended lymphadenectomy. Mean time CT and surgery=25.4 days, between PET and surgery =30 days	36 bone scintigraphy were available to compare with FDG PET-CT. Both detected the 3 patients with bone mets. In one case an additional pelvic and vertebral bone mets were detected by FDG PET-CT only.		33 had CT and PET/CT, 11 had only PET/CT. Study also included in topic D1 and D3.
Yang 2012 China	Retrospective study	Moderate risk of bias, consecutive sample used, index test was interpreted with knowledge of clinical history and other imaging results, not all patients received same reference standard (biopsy or further imaging).	60 consecutive patients with a history of bladder cancer referred 2006-2010 for whole body FDG PET-CT scans.	Male 77%, female 23%. Median age 60.5 (range 32-96) 22 N0, 27 N1, 11 N2. 16 had cystectomy, 44 had chemo, radiotherapy or chemo/radiotherapy. 25 routine follow-up scan, 22 detection of suspected mets, 13 monitoring.	Whole body FDG PET-CT using Explora FDG_4 module. All required to fast for at least 6h. Scanning 1h after administration of tracer (7.4MBq/kg). Images obtained on Siemens biograph 16HR PET-CT scanner. Abnormal FDG uptake was defined as radiotracer accumulation that was thought to be outside of normal anatomical structures. SUVmax for each lesion was calculated. Reviewing physicians were aware of clinical history and other imaging.	All suspicious PET-CT lesions were assessed further using biopsies or subsequent imaging. 24 verified by biopsy, 100 validated by serial imaging or other clinical examinations for at least 6 months (98 CT, 12 MRI) For bone mets, bone scintagraphy and AKP were applied as complementary	Suspicious bone lesions (n=9, 6.9%) TP 9 TN 0 FP 0 FN 0 Change in management in 15 patients (25%)	Sens 100 Spec N/A PPV 100 NPV n/a	Organ based analysis of sensitivity and specificity. Study also included in topic D3

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
Davey 1985 UK	Retrospective review	Moderate risk of bias, consecutive sample used, unclear if index test was blind to other results, reference standard unclear and unclear if all patients received same ref standard,	221 consecutive patients with invasive bladder cancer suitable for RT who had bone scintigraphy as part of tumour staging 1975-1982	155 males, 66 females. Mean age 69 years. 37 T1, 24 T2, 65 T3a, 52 T3b, 21 T4a, 19 T4b, 3 Tx	Bone scintigraphy on Cleon multidetector scanner 3-5h following 750MBq (19mCi) technetium-99m methylene diphosphonate. Entire skeleton images obtained. Plain radiographs were obtained of any area to which local symptoms were referable, irrespective of scintigraphic findings and of all scintigraphically suspect areas. Scintigraphs were classified as normal if no abnormality of distribution of radioactivity, 'non-significant abnormality' if radiographs demonstrated a possible benign cause for a focal increase in uptake, 'equivocal' if radiographic appearances were non-specific, and 'abnormal' if radiographs confirmed metastatic bone involvement or if there was no benign explanation for focal increase in concentration of radiotracer.	Clinical and radiological follow-up (not specified)	86 (39%) examinations had increased uptake of radiotracer, majority due to non-malignant conditions. 14 (6%) had abnormal bone scintigrams considered to be consistent with metastases. 4/14 did not develop clinical, radiographic or biochemical evidence of skeletal disease during the course of disease. 3 alive at 7, 44 and 49 months. One died with no bone mets found at post-mortem. 6/10 patients who developed bone mets as predicted by their scintigram were treated radically. 16/207 (8%) with non-significant or normal scintigrams at presentation developed clinical or radiographic evidence of skeletal secondaries (10 within 12 mo).	**Sensitivity of scintigraph at diagnosis:** 38% (10/26) **Incidence:** 12% **Negative predictive value:** 92% (100%-8%)	

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
Chakrabort y 2013 India	Prospective comparative study	Low risk of bias, consecutive sample used, bone scan blinded to pathology and other clinical information, unclear if ref standard interpreted without knowledge of imaging, not all patients had same ref standard.	48 consecutive patients with newly diagnosed locoregional or metastatic bladder cancer and with high likelihood of bone mets (muscle invasion, history of bone pain, raised alkaline phosphatase, lytic lesions on xray)	44 male, 4 female. Median age 60 yrs (range 35-80) 12 had bone pain, 25 showed raised alkaline phosphatase	Tc-MDP bone scintigraphy followed by F-fluoride PET/CT within 48 hrs. Whole body bone scan 3-4h after i.v. injection of 20-25mCi 910MBq/kg) of Tc-MDP. Planar images on duel headed gamma camera. SPCET/CT imaging performed only for specific areas in case of any suspicious foci detected on the planar image. F-Fluoride PET/CT from skull to upper thighs 45min after contrast i.v. injection using a Discovery STE 16 PET/CT scanner. In patients showing symptoms of bony pain in lower extremities, an additional image from foot to thigh was acquired. Findings of bone scan were interpreted before PET/CT scan. Blind to path reports and other clinical information.	Metastatic bony involvement was verified by histological correlation where possible. Alternatively clinical follow-up and/or contrast enhanced CT/MRI/skeletal survey correlation was used to confirm mets. Follow-up bone scan 6-12mo after initial scan established true negatives. 17 (35%) were finally diagnosed with bone mets based on definitive biopsy and imaging follow-up	**F-fluoride PET-CT** **TP** 17 **FP** 4 **TN** 27 **FN** 0 **Tc-MDP SPECT/CT** **TP** 15 **FP** 8 **TN** 23 **FN** 2 **Tc-MDP planar BS** **TP** 14 **FP** 11 **TN** 20 **FN** 3 **Change in management:** 17 patients with mets changed to systemic chemo and bisphosphonate therapy.	**F-fluoride PET-CT** **Sens** 100 **Spec** 87 **PPV** 81 **NPV** 100 **Tc-MDP SPECT/CT** **Sens** 88 **Spec** 74 **PPV** 65 **NPV** 92 **Tc-MDP planar BS** **Sens** 82 **Spec** 65 **PPV** 56 **NPV** 87	Patient based analysis. PET-CT not in PICO.
Balliu 2010 Spain	Prospective comparative study	Low risk of bias, Image review blinded, population not all relevant to PICO, random sample of patients, not all patients received same reference standard, time between index	38 randomly selected patients with primary malignant solid tumours (breast and lung) or other malignant tumours and clinical signs and symptoms suggestive of bone mets.	27 men, 11 women. Mean age 62.1 ±14 yrs Lung (n=11), breast (n=8), bladder (n=4), myeloma (n=2), colon (n=2), germ cell (n=1), endometrial (n=1), renal (n=1), gallbladder (n=1). Symptoms of bone mets (n=29, 76%)	**Bone scan:** 2 hrs after i.v. injection of 925 mBq (25mCi) of HMDP tagged with 99 m technetium using high resolution, dual head gamma camera with low energy collimators, Planar images also acquired when deemed necessary. Tomographic studies or SPECT images were also acquired over the region of interest. **Whole body MRI:** 1.5 T, Q body coil with at least 5 stations, and	Findings verified by at least 12mo clinical follow-up, additional imaging tests, and/or biopsy (when biopsy clinically indicated)	Bone mets present in 18 (47%) **Bone scan** **TP** 13 **FP** 5 **TN** 15 **FN** 5 **MRI** **TP** 17 **FP** 2 **TN** 18	**Bone scan:** **Sens** 72 **Spec** 75 **PPV** 72 **NPV** 75 **MRI:** **Sens** 94 **Spec** 90 **PPV** 89 **NPV** 95	Patient level analysis of sensitivity and specificity. Higher inter-observer agreement for MRI than bone scan.

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
		test and ref standard unclear.	Each week the first 2 patients were selected among all patients meeting the inclusion criteria 2006-2007.		the possibility of changing parameters in each one. Coronal T1WI, coronal STIR sequence. Images analysed using a ViewForum workstation using sagittal and axial multiplanar reconstructions of the entire spine and other area of interest in a given study. Findings classified using a 4-point scale (1-2 considered negative, 3-4 positive).		**FN** 1		
Brismar 1988 Sweden	Appears prospective	Moderate risk of bias, unclear if random or consecutive sample used, reference standard not reported, unclear if all patients received same ref standard, unclear if index test and ref standard were blind to other results	71 patients staging MIBC, 67 of these had no symptoms, 4 had skeletal pain. 26 patients previously treated for bladder cancer, without known dissemination, presented with signs or symptoms suggestive of skeletal mets - pain in 23, 1 leg paresis, 1 leg weakness, 1 lumbar stiffness. 1984-1987	14 female, 57 male. Mean age 67 years	**Bone scintigraphy:** 3-5hrs after 370MBq of ^{99}Tc-MDP whole body registration performed in anterior and posterior projections using General Electric Maxicamera equipped with a general purpose low energy collimator. In patients with normal findings or only typical osteoarthritic changes, no skeletal radiographs were obtained. In patients with scintigraphic signs of mets or with equivocal findings, correlating skeletal films were obtained. All scintigrams were classified as no mets or mets. Areas of increased uptake which corresponded to regions of known trauma or were explained as osteoarthritic from corresponding radiographs or had distribution or appearance typical of degenerative changes were classified as 'no mets'.	Compared with previous and new correlating radiographs and after utilizing available clinical information concerning, for example, recent trauma.	**Results of scintigraphy:** 1) no signs or symptoms (n=67): 1 suggested mets which was false positive (negative biopsy). In 5 patients increased uptake was explained as being due to osteoarthritic lesions. In 7 patients a repeat scan was performed due to symptoms – mets were found in 3 patients, 7, 10, and 16 mo after negative staging bone scan. 2) patients with signs/symptoms (n=30): 7 were true positives and 1 patient had increased uptake which was not confirmed on autopsy (false positive)		Sensitivity and specificity not reported. Results from bone scintigraphy included supplementary radiographs.
Braendeng en 1996	Retrospective series	Moderate risk of bias, not a	Of 227 consecutive	66 male, 25 female. Median age 64	**Bone scintigram:** Whole body scan with gamma camera	Follow-up consisted of	In 31 patients, skeletal radiography was performed to determine the nature of the		Sensitivity and specificity not

Reference	Study type	Study quality	N patients	Patient characteristics	Test	Reference standard	Raw data for 2x2 table	Sensitivity, specificity, PPV, NPV (%)	Additional comments
Norway		consecutive or random sample, index test not blind to other results, not all patients received same reference standard,	patients with MIBC and no distant mets underwent total cystectomy, 91 had pre-cystectomy bone scan. None had clinical suspicion of bone metastases.	(range 34-75). 31 T2, 58 T3, 2 T4a. None had suspicion of skeletal mets based on history or clinical findings.	obtained 2.5h after i.v. injection of 550 mBq of ^{99}Tc-MDP together with additional restricted views covering the trunk. In patients with doubtful extent of uptake on bone scan, a radiograph of affected bones was taken to determine cause of pathological changes. All scans were evaluated by a nuclear medicine physician using a nuclear medicine code (NMC) prospectively: I = No pathological abnormality. II = Probable degenerative abnormality. III = Hot spots suspicious of malignancy. IV = Hot spots of significant increased uptake, of probable malignant origin. These gradings were not added to the patients' records and were not seen by the clinicians involved in the care of the patient. Scans were instead viewed by the patient's clinician and graded according to the following Clinical Code (CC): I = No pathology. II = Increase uptake, not caused by malignancy. III = Increase uptake suspicious of malignancy. IV = Pathological uptake, most probably owing to metastases. If the oncologist graded the scan as being suspicious of malignancy, a radical cystectomy was not performed.	clinical exam, blood analysis, skeletal radiology, or other specialised tests if clinically indicated. Follow-up was every 3 to 6 months for 5 years and every 12 months thereafter.	pathological uptake on the bone scan. 13 had bone scans with uptake probably due to metastases and in 12 of these the radiographs showed a non-pathological fracture or benign degenerative changes. No radiological abnormalities were found in remaining patient. 8 patients were given a Nuclear Medicine Code (NMC) III (suspicious of metastases), in 3 of these radiology was normal, degenerative changes were diagnosed in 5. 42 patients coded NMC II (degenerative changes), 9 had radiography which showed normal findings in 2, degenerative changes in 6, and a non-pathological fracture in 1. During follow-up, 37 patients (40.7%) were diagnosed with metastatic bone disease. It is unclear if this included all of the patients whose bone scans were coded as having metastatic disease by the nuclear medicine physicians (35 patients) or by the clinicians (22 patients). Risk of subsequent bone mets was unrelated to T category. 5-yr survival for NMC I (minimal changes, not compatible with pathology) =70%. NMC IV (uptake probably due to mets) = 30%. In 3/54 patients referred for cystectomy, the pre-operative bone scan and subsequent radiographs confirmed presence of bony mets and lead to decision not to perform total cystectomy. In the remaining 51 the results of the bone scan did not contribute to final therapeutic decision. 27 patients did not undergo RC because of indications of inoperability other than bone scan results.		reported. Unclear how many patients were considered to actually have bone mets from the bone scan (i.e. number of true positives).

3 Manageing non-muscle-invasive bladder cancer

3.1 Risk Stratification

3.1.1 Prognostic markers in NMIBC

Review question: In addition to the factors specified in the EORTC risk tables, do TCC variants, differentiation of TCC and lymphovascular invasion predict recurrence and progression after treatment?

Rationale

In general, recurrence is a problem for patients (because any tumour recurrence raises the concern that the cancer will progress and/or spread) and for the NHS (because of the need to provide capacity for treatment of recurrence), but it does not threaten patients' lives. In contrast, progression does threaten patients' lives, because if the muscle coat of the bladder becomes involved with cancer, between 20 and 25 out of 100 such patients will have spread into their lymph glands, and their chance of cure falls sharply.

We have some pathological markers of the risks of recurrence and progression, such as stage, grade, and the presence of carcinoma *in situ*, and other clinical markers, such as tumour size, number and the presence of recurrence at three months from the initial resection. On the basis of EORTC chemotherapy study data, it was suggested many years ago that the management of LRNMIBC could be streamlined significantly by the use of two easily established clinical variables alone, namely whether the initial tumour is solitary or multifocal, and whether there was recurrence or not at three months. Despite the evidence base for this, and its ease of assessment, it has not become widely used in the NHS.

So the use of these factors remains unsatisfactory for an individual patient, and does not predict the individual risks of recurrence and progression. Molecular markers (such as EGFR) have been studied for over 20 years, to see if some laboratory studies are able to be useful in clinical practice, but none has emerged as useful to the NHS.

If we knew better for individual patients about their risk of recurrence and particularly progression, it would be possible to inform the discussion of the cancer risk, which is one of the pillars of the discussion about which treatment option is best for a given patient. Many patients would consider better forecasting of their own personal cancer risk to be a very useful step forward.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with newly diagnosed NMIBC	Prognostic factors: EORTC risk factors TCC variants (micropapillary and nested patterns) TCC differentiation (squamous, glandular and sarcomatoid) Lymphovascular invasion	N/A	• Disease specific survival • Recurrence • Overall survival • Disease progression

METHODS

Information sources

A literature search was conducted by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. Validation studies of the EORTC risk calculator were selected if there were sufficient numbers of patients in each risk category to allow a meaningful validation. Prognostic studies of the other factors in the PICO (TCC variants, TCC differentiation, lymphovascular invasion) were also appraised.

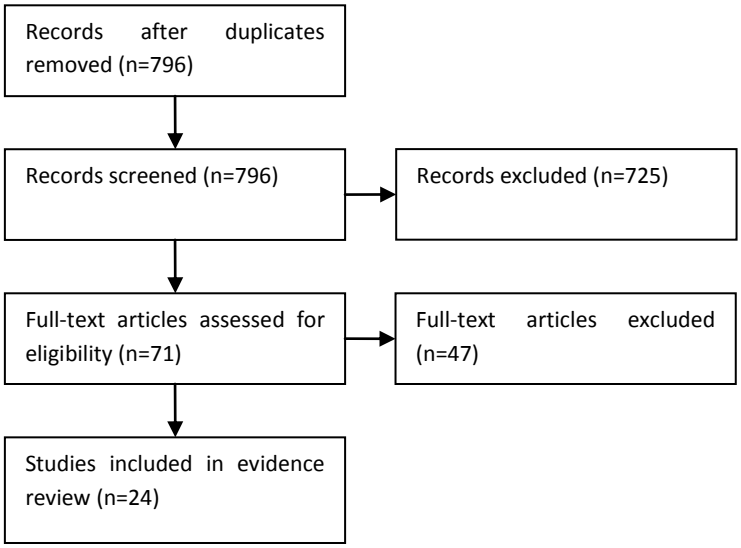
Data synthesis

The results are presented by outcome and by prognostic factor. Hazard ratios and *p* values are provided as reported in the studies. The validation studies of the EORTC risk factors are also presented with c-indices and estimated and observed numbers of recurrences and progressions.

RESULTS

Result of the literature searches

Figure 30. Study flow diagram



Study quality and results

The NICE prognostic studies methodological checklist was used to assess the quality of the prognostic studies. All studies were assessed as being of high quality as they included the population of interest, measured the outcome adequately, and used appropriate statistical analysis. However, validation studies of the EORTC risk tables were limited by heterogeneous patient populations and treatments received and by low numbers of progression events. Studies exploring

the prognostic factors of lymphovascular invasion, TCC variants and TCC differentiation were limited by small sample sizes and few patients with the factor under investigation. The results of the study quality assessment is provided in Table 30. The results of the included studies are summarised in Tables 26-33 and Figures 31-35.

Table 30. Study quality assessment

Study	Quality criteria						Quality
	Sample represents the population of interest?	Loss to follow-up unrelated to key characteristics?	Prognostic factor adequately measured?	Outcome adequately measured?	Confounders accounted for?	Appropriate statistical analysis used?	
Sylvester 2009	y	y	y	y	y	y	high
Fernandez-Gomez 2008	y	y	y	y	y	y	high
Lopez 1995	y	y	y	y	y	y	high
Scosyrev 2009	y	y	y	y	y	y	high
Cho 2009	y	y	y	y	y	y	high
Brimo 2013	unclear	y	y	y	y	y	high
Miyake 2011	y	y	y	y	y	y	high
Kwon 2012	y	y	y	y	y	y	high
Palou 2012	y	y	y	y	y	y	high
Sakano 2010	y	y	y	y	y	y	high
Tilki 2012	y	y	y	y	unclear	y	high
Branchereau 2013	y	y	y	y	unclear	y	high
Olsson 2013	y	y	y	y	y	y	high

Narrative summary of evidence

EORTC risk factors: Recurrence & Progression

The European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Group published risk tables that provide the probabilities that a patient with superficial bladder cancer (Ta,T1) will recur or progress to muscle-invasive disease after transurethral resection of the bladder tumour (TURBT) (Sylvester, 2006). Seven randomised trials including 2596 patients and with a maximum follow-up of 15 years were included in the analysis by Sylvester (2006). 6% of patients were randomised to intravesical bacillus Calmette-Guérin (BCG) and none of the patients received maintenance therapy. The EORTC scoring system was derived based on six clinical and pathological factors: number of tumours, tumour size, prior recurrence rate, T category, carcinoma in situ (CIS), and grade. Fernandez-Gomez (2011) reported a validation of the EORTC risk tables in a cohort of 1062 patients treated with BCG from 4 randomised trials (CUETO studies). 73% of this cohort received 10-12 BCG instillations. The EORTC risk tables successfully divided CUETO patients into four risk groups for recurrence and progression.

The c-indices for recurrence were similar in the EORTC and CUETO series. For recurrence the PSEP in the CUETO series was lower than the EORTC at 1-year (0.3/0.26 vs. 0.46), similar results were found at 5-years (0.49/0.51 vs. 0.47). For progression, the c-index in the CUETO cohort was 0.69 at 1-year and 0.68 at 5-year, which are lower than the EORTC c-indices for progression at 1-year (0.74) and 5-years (0.75). The PSEP in the CUETO series was lower than the EORTC for progression at 5-years (0.25 vs. 0.442). Xylinas (2013) presented a validation study of 4689 patients, and reported c-indices which demonstrated poor discrimination of the EORTC risk models for recurrence and progression.

In 7 validation studies (Fernandez-Gomez 2011; Seo 2010; Altieri 2012; Hernandez 2011; van Rhijn 2010; Xu 2013; Lammers 2014), the EORTC risk tables generally overestimated the risk of recurrence in all risk groups and the risk of progression at 5-years especially in high risk groups. However, many of these studies were limited by a low number of progression events. In an earlier report from the CUETO cohort, Fernandez-Gomez (2008) reported that, in multivariate analysis, female gender (HR=1.71) compared to male gender, recurrent tumours (HR=1.9) compared to primary tumours, multiplicity, and presence of associated tumour in situ (TIS) (HR=1.55), were significant independent factors for recurrence. For progression, recurrent tumours (HR=1.62) compared to primary tumours, high-grade tumours (HR=5.64) compared to G1 tumours, T1 tumours (HR=2.15) compared to Ta tumours, and recurrence at 3-month cystoscopy (HR=4.6) were independent predictive factors.

One study of 592 Japanese patients, half of whom received no intravesical therapy after TURBT, attempted to validate the EORTC risk scores for recurrence (Sakano, 2010). There was only a significant difference in recurrence-free survival when the low-risk and intermediate-low risk groups were combined into one group, and the intermediate-high risk and high risk groups were considered as another group. Multivariate analysis showed that prior recurrence rate, number of tumours, and T category were independent predictors for time to first recurrence.

In another validation study including 230 patients with primary non-muscle invasive bladder cancer (van Rhijn, 2010), EORTC risk scores for progression and recurrence were significant factors in multivariate analysis. However, none of the patients in this cohort were at high risk of recurrence and all patients had primary NMIBC, which limits the usefulness of this study. One study of patients with T1 bladder cancer, all of whom were treated with BCG, reported that EORTC risk scores were not significant predictors of progression or recurrence (van Rhijn, 2012). Multiplicity was the most important variable for predicting recurrence, whilst sub-stage (T1m/T1e), female gender and CIS were the most important variables for progression in multivariate analysis.

One prognostic study of 146 patients with T1G3 NMIBC treated with an induction course of BCG reported that female gender and presence of CIS in the prostatic urethra were associated with an increased risk of recurrence, progression and disease-specific mortality (Palou, 2012).

Lymphovascular invasion: Recurrence and progression

Seven studies included lymphovascular invasion as a prognostic factor for recurrence or progression (Brimo 2013; Miyake 2011; Kwon 2012; Cho 2009; Tilki 2012; Park 2009; Olsson 2013). Some studies reported that the presence of lymphovascular invasion was a prognostic factor for recurrence or progression and some studies reported no significant effect in univariate and multivariate analyses (see Figures 31-35 below for forest plots of reported hazard ratios from univariate and multivariate analyses). Analysis of this factor was limited by the low number of patients with invasion. Park

(2009) reported that lymphovascular invasion was not a predictor of recurrence or progression in patients with T1G3 bladder cancer who received BCG therapy (HRs were not reported so could not be included in the forest plots).

Lymphovascular invasion: Disease-specific survival

Two studies (Lopez, 1995; Tilki, 2012) reported that lymphovascular invasion was an independent prognostic factor for disease-specific survival and one study reported no significant effect (Olsson, 2013) (see Figure 35).

Lymphovascular invasion: Overall survival

One study of 108 patients (Branchereau 2013) reported that lymphovascular invasion was an independent prognostic factor for overall survival for patients with high grade T1 tumours (p=0.003, HR not reported).

Histological subtype ('usual TCC' vs. micropapillary/sarcomatoid TCC): Recurrence and progression

One study (Brimo, 2013) reported that adverse histological variants were significantly associated with progression and recurrence on univariate analysis but were insignificant on multivariate analysis. Only 4 tumours were not 'usual' TCC. 3 had features of micropapillary TCC and 1 had features of sarcomatoid TCC.

Histological subtype (TCC vs. squamous cell carcinoma): Overall survival and disease specific survival

Scosyrev (2009) reported that squamous cell histologic features were associated with overall mortality and disease-specific mortality compared to TCC in patients who did not undergo cystectomy, but was not associated with increased mortality in those who were treated with cystectomy.

Micropapillary pattern (MPP): Progression

One study (Alkibay, 2009), reported that progression rates increased in patients with NMIBC and MPP compared with MPP-negative patients but this difference was not statistically significant (p=0.064). This analysis was based on only 6 patients with T1 bladder cancer and MPP, and 125 TaT1 MPP-negative patients.

Evidence statements

The EORTC risk tables (Sylvester *et al.*, 2006) have been validated in several studies, which report that the tables successfully stratify patients into risk groups for recurrence and progression, but generally overestimate the risk of recurrence in all risk groups and the risk of progression in high risk groups (Fernandez-Gomez *et al.,* 2011; Seo *et al.,* 2010; Altieri *et al.,* 2012; Hernandez *et al.,* 2011; van Rhijn *et al.,* 2010; Xu *et al.,* 2013; Lammers *et al.,* 2014).

There is some low quality evidence to suggest that the presence of lymphovascular invasion increases the risk of recurrence, progression and disease-specific survival. However, this is based on low numbers of patients with evidence of lymphovascular invasion.

One study (Brimo *et al.*, 2013) reported that adverse histological variants were significantly associated with progression and recurrence on univariate analysis but were insignificant on multivariate analysis. Only four tumours were not 'usual' TCC. Three had features of micropapillary TCC and one had features of sarcomatoid TCC.

One study (Scosyrev *et al.*, 2009) reported that squamous cell histologic features were associated with overall mortality and disease-specific mortality compared to TCC in patients who did not undergo cystectomy, but was not associated with increased mortality in those who were treated with cystectomy.

One study (Alkibay *et al.*, 2009), reported that progression rates increased in patients with NMIBC and micropapillary pattern (MPP) compared with MPP-negative patients but this difference was not statistically significant (p=0.064). This analysis was based on only six patients with T1 bladder cancer and MPP, and 125 TaT1 MPP-negative patients.

Table 31. Univariate and multivariate analyses of recurrence

Study (n patients)	Follow-up	Prognostic factor	Univariate analysis			Multivariate analysis			
			HR	95% CI	p-value	HR	95% CI	p-value	Factors adjusted for
Recurrence									
Sylvester 2006 N=2596	Median 3.9 yrs, maximum 14.9 yrs	Age: ≤65 years, >65 years	1.10		.089				Univariate and multivariate model stratified by study and the presence or absence of intravesical treatment
		Gender: male, female	1.00		.986				
		Prior treatment: no, yes	**1.31**		**.013**				
		Tumour status: primary, recurrent	**1.67**		**<.0001**				
		Prior recurrence rate: primary, recurrent ≤1rec/yr, >1rec/yr	**1.42**		**<.0001**	**1.35**	**1.24 to 1.46**	**<.0001**	
		Number of tumours: single, multiple	**1.96**		**<.0001**				
		Number of tumours: single, 2-7, ≥8	**1.71**		**<.0001**	**1.56**	**1.42 to 1.71**	**<.0001**	
		Tumour size: <3cm, ≥3cm	**1.34**		**<.0001**	**1.54**	**1.32 to 1.80**	**<.0001**	
		T category: Ta, T1	**1.37**		**<.0001**	**1.21**	**1.07 to 1.37**	**.003**	
		Carcinoma in situ: no, yes	**1.40**		**.008**	1.19	.924 to 1.52	.180	
		Grade: G1, G2, G3	**1.29**		**<.0001**	**1.17**	**1.07 to 1.28**	**.001**	
		Grade G3: no, yes	**1.42**		**<.0001**				
		T1G3: no, yes no CIS, yes CIS	**1.48**		**<.0001**				
Van Rhijn 2010 N=230	Median 8.6 yrs	EORTC recurrence score	-	-	**.005**	**2.53**	**1.48-4.17**	**.001**	Age, gender, hospital, CIS, multiplicity, tumour size, grade, stage, EORTC risk scores, and molecular grade

Van Rhijn 2012 N=129	Median 6.5 yrs	EORTC recurrence score			.413	1.14	0.43 to 3.02	.789	
Fernandez-Gomez 2008 CUETO series N=1062	Median 69 months	Gender: male, female	**1.80**	**1.33 to 2.44**	**.0001**	**1.71**	**1.26 to 2.33**	**0.0006**	Univariate and multivariate model stratified by study and dose to assess the independent effects of several variables
		Age: ≤60	1	-	**.0151**				
		61-70	**1.30**	**0.99 to 1.70**					
		>70	**1.50**	**1.14 to 1.98**					
		Recurrent tumour: no, yes	**2.05**	**1.65 to 2.54**	**<.0001**	**1.90**	**1.53 to 2.37**	**<.0001**	
		No. of tumours: 1	1	-	**<.0001**	1	-	**.0110**	
		2-3	1.28	0.98 to 1.66		1.11	0.85 to 1.45		
		4-7	**1.74**	**1.29 to 2.34**		**1.43**	**1.06 to 1.94**		
		≥8	**2.15**	**1.53 to 3.01**		**1.67**	**1.18 to 2.37**		
		Size: ≤1cm	1	-	.0502				
		1-3cm	0.70	0.52 to 0.93					
		≥3cm	0.84	0.65 to 1.08					
		Grade: G1	1	-	.4532				
		G2	1.04	0.46 to 1.42					
		G3	1.27	0.84 to 1.93					
		Stage: Ta, T1	1.04	0.79 to 1.36	.7787				
		Associated TIS: no, yes	**1.63**	**1.12 to 2.36**	**.0105**	**1.55**	**1.06 to 2.26**	**.0239**	
Sakano 2010 N=592	Median 37 months	Age: ≤70 years, >70 years	**1.20**	**1.06 to 1.35**	**.003**	1.03	0.88 to 1.21	.70	
		Gender: male, female	0.97	0.84 to 1.11	.68				
		Prior recurrence rate: primary, recurrent	1	-	**.002**	1	-	**.046**	
		<1rec/yr,	**1.12**	**0.97 to 1.29**		**1.12**	**0.94 to 1.33**		
		≥1rec/yr	**1.31**	**1.12 to 1.52**		**1.26**	**1.04-1.52**		

		Number of tumours: single, 2-7 ≥8	1 **1.33** **1.43**	- **1.19 to 1.49** **1.07 to 1.84**	**<.001**	1 **1.40** 1.15	- **1.21-1.62** 0.76-1.64	**<.001**	
		Tumour size: ≤3cm, >3cm	1.04	0.77 to 1.34	.80				
		T category: Ta, T1	**1.17**	**1.05 to 1.31**	**.004**	**1.17**	**1.00 to 1.36**	**.044**	
		Carcinoma in situ: no, yes	0.94	0.77 to 1.14	.56				
		Histopathology: pure UC, UC with other elements	0.98	0.68 to 1.33	.92				
		Grade: G1, G2, G3	1 **1.29** **1.40**	- **1.09 to 1.13** **1.16 to 1.69**	**<.001**	1 1.22 1.37	- 0.98 to 1.54 1.01 to 1.87	.21	
		Intravesical therapy: No, Chemotherapy BCG	1 1.01 0.87	- 0.89 to 1.13 0.73 to 1.02	.18				
Palou 2012 N=146 T1G3	Median 104 months	Age(years): ≤65, >65 ≤60, 61-65, 66-70, >70	 1.34 1.11	 0.82 to 2.18 0.91 to 1.36	 .24 .32	 - -	 	 NS 	Age, number of tumours, tumour size, tumour aspect, CIS, and the combined variable "CIS in the prostatic urethra or female"
		Gender: male, female	2.30	1.25 to 4.27	.008	NA			
		Number of tumours: single, multiple	1.16	0.71 to 1.89	.54	-		NS	
		Size: ≤1.5cm, 1.5-3cm, >3cm	1.16	0.84 to 1.60	.36	-		NS	
		Tumour aspect: papillary, solid	1.26	0.74 to 2.13	.39	-		NS	
		T1 substage: T1a, T1b, T1c	1.08	0.78 to 1.49	.64	NA			

		Concomitant CIS: no, yes	0.98	0.59 to 1.62	.93	-		NS	
		CIS in prostatic urethra: no, yes	**2.40**	**1.16 to 4.95**	**.02**	NA			
		CIS in prostatic urethra: no, yes, female	-		**.001**	NA			
		CIS in prostatic urethra or female: no, yes	**2.53**	**1.50 to 4.25**	**.0003**	**2.53**	**1.50 to 4.25**	**.0003**	
Park 2009 N=144 T1G3	Median 52.5 months	Age: < median age, ≥median age			.205				
		Sex: male, female			.142				
		CIS: yes, no			.497				
		Multiplicity: single, multiple			.894	1.109	0.64 to 1.93	.714	
		Size: <3cm, ≥3cm			.290	0.755	0.43 to 1.32	.321	
		Lymphovascular invasion: no, yes			.529				
		Gross morphology: papillary, non-papillary			.879				
		Microscopic morphology: papillary, non-papillary			.079	1.456	0.88 to 2.41	.144	
		Intravesical therapy: no, yes			**.0001**	**0.328**	**0.18 to 0.59**	**<.001**	
		Proper muscle: absent, present			.603	1.127	0.63 to 2.00	.684	
Brimo 2013 N=86	Mean 29 months	Lymphovascular invasion: no, yes	1.76	0.82 to 3.77	.146	1.13	0.44 to 2.93	.806	
		Adverse histological subtype: 'usual' UC, micropapillary/sarcomatoid UC	**5.94**	**2.01 to 17.6**	**.001**	3.20	0.81 to 12.77	.100	

		Carcinoma in situ: no, yes	1.41	0.79 to 2.51	.250	1.25	0.67 to 2.31	.481	
		Maximum tumour diameter (mm)	**1.17**	**1.03 to 1.32**	**.013**	1.14	0.95 to 1.37	.157	
Cho 2009	Median 35 mo, range	Lymphovascular invasion: no, yes	1.69	0.90 to 3.02	.086	**2.02**	**1.11 to 3.90**	**.029**	
N=118	12-89 mo	Gender: female, male	2.09	0.75 to 5.83	.160				
		Age: <65, ≥65	1.02	0.55 to 1.90	.945				
		Bladder tumour history: no, yes	**3.38**	**1.81 to 6.32**	**<.001**	**3.41**	**1.74 to 6.67**	**<.001**	
		Size: <3cm, ≥3cm	**1.95**	**1.08 to 3.50**	**.026**	**1.995**	**1.06 to 3.74**	**.031**	
		Number of tumours: <4, ≥4	**2.54**	**1.35 to 4.78**	**.004**	**1.97**	**1.02 to 3.81**	**.043**	
		Grade: 1&2, 3	1.20	0.67 to 2.16	.536				
		Carcinoma in situ: no, yes	1.18	0.28 to 4.88	.823				
		Intravesical therapy: no, yes	1.98	0.95 to 4.12	.069	1.095	0.48 to 2.48	.828	
Kwon 2012	Median 77 mo, range	Lymphovascular invasion: no, yes			**.002**	1.50	0.55 to 4.08	.427	
N=406	12-167 mo	Age				1.03	1.0 to 1.06	.235	
		Gender				1.26	0.94 to 1.71	.129	
		Stage: Ta, T1			**.001**	0.71	0.44 to 1.16	.169	
		Grade: low, high				**1.32**	**1.04 to 1.66**	**.022**	
		Size: <3cm, ≥3cm				1.59	0.83 to 3.04	.164	

		Multiplicity: ≤3, >3			**.024**	**1.62**	**1.07 to 2.69**	**.043**	
Miyake 2011 N=130	Median 36 mo, range 1-140 mo	Lymphovascular invasion: no, yes	1.75	0.86 to 4.93	.11				
		Stage: Ta, T1	1.40	0.68 to 3.21	.32				
		Grade (WHO 2004):							
		PUNLMP	1	-	-				
		LG	1.41	0.50 to 4.00	.57				
		HG	2.17	0.70 to 5.56	.2				
		Concomitant CIS: yes, no	1.32	0.36 to 5.28	.20				
		Multiplicity: solitary, multiple	**1.91**	**1.04 to 3.59**	**.038**	1.93	0.98 to 3.79	.058	
		Tumour diameter: <3cm, ≥3cm	**2.04**	**1.13 to 5.06**	**.023**	**2.10**	**1.04 to 4.27**	**.040**	
		Intravesical therapy:							
		None	1	-	-	1	-	-	
		BCG	**0.53**	**0.23 to 0.96**	**.039**	**0.35**	**0.18 to 0.71**	**.004**	
		Anthracyclines	0.96	0.28 to 3.21	0.94	0.63	0.24 to 2.38	.63	
Tilki 2012 N=101	Median 38 months	Lymphovascular invasion: no, yes			**<.001**	**4.9**	**1.4 to 16.5**	**0.01**	
		Stage: T0,Ta, Tis T1				**8.5**	**1.1 to 67**	**0.04**	
Olsson 2013 N=211	Median 60 months	Lymphovascular invasion no, yes	**2.63**	**1.48 to 4.66**		**2.36**	**1.31 to 4.28**	**0.005**	

Table 32. Univariate and multivariate analyses of progression

Study (n patients)	Follow-up	Prognostic factor	Univariate analysis			Multivariate analysis			
			HR	95% CI	p-value	HR	95% CI	p-value	Factors adjusted for
Progression									
Sylvester 2006 N=2596	Median 3.9 yrs, maximum 14.9	Age: ≤65 years, >65 years	**1.36**		**0.012**				Univariate and multivariate model stratified by study and the presence or absence of intravesical treatment
		Gender: male, female	0.92		0.580				
		Prior treatment, no, yes	1.19		0.442				
		Tumour status: primary, recurrent	**1.36**		**0.036**	**1.48**	**1.07 to 2.03**	**0.016**	
		Prior recurrence rate: primary, recurrent ≤1rec/yr, >1rec/yr	**1.19**		**0.027**				
		Number of tumours: single, multiple	**1.86**		**<.0001**	**1.70**	**1.29 to 2.24**	**0.0002**	
		Number of tumours: single, 2-7, ≥8	**1.48**		**<.0001**				
		Tumour size: <3cm, ≥3cm	**1.94**		**<.0001**	**1.89**	**1.40 to 2.55**	**<.0001**	
		T category: Ta, T1	**2.80**		**<.0001**	**2.19**	**1.67 to 2.86**	**<.0001**	
		Carcinoma in situ: no, yes	**4.19**		**<.0001**	**3.41**	**2.32 to 5.01**	**<.0001**	
		Grade: G1, G2, G3	**2.40**		**<.0001**				
		Grade G3: no, yes	**3.88**		**<.0001**	**2.67**	**1.99 to 3.59**	**<.0001**	
		T1G3: no, yes no CIS, yes CIS	**4.00**		**<.0001**				
		Recurrence at 3 months: no, yes	**3.11**		**<.0001**				
Van Rhijn (2010)	Median 8.6 yrs	EORTC progression Low vs. Intermediate risk	- -	-	**.001**	**-** **1.84**	**-** **0.96-3.59**	**.001** **.194**	Age, gender, hospital, CIS, multiplicity, tumour

Study (n patients)	Follow-up	Prognostic factor	Univariate analysis			Multivariate analysis			
			HR	95% CI	p-value	HR	95% CI	p-value	Factors adjusted for
Progression									
N=230		Low vs. High risk				**4.52**	**1.41-7.58**	**<.001**	size, grade, stage, EORTC risk scores, and molecular grade
Van Rhijn 2012 N=129	Median 6.5 years	EORTC progression			.163	1.38	0.37 to 5.12	.628	
Fernandez-Gomez 2008 N=1062	Median 69 months	Gender: male, female	1.01	0.58 to 1.76	.98				Univariate and multivariate model stratified by study and dose to assess the independent effects of several variables
		Age: ≤60	1	-	**.0174**	1	-	.052	
		61-70	**1.74**	**1.12 to 2.71**		1.57	1.00 to 2.45		
		>70	**1.86**	**1.81 to 2.94**		1.74	1.20 to 2.75		
		Recurrent tumour: no, yes	**1.52**	**1.09 to 2.14**	**.015**	**1.63**	**1.14 to 2.32**	**.0068**	
		No. of tumours: 1	1	-	.3625				
		2-3	1.13	0.75 to 1.70					
		4-7	1.27	0.78 to 2.06					
		≥8	1.59	0.93 to 2.70					
		Size: ≤1cm	1	-	.4147				
		1-3cm	0.75	0.48 to 1.17					
		≥3cm	0.83	0.56 to 1.22					
		Grade: G1	1	-	**<.0001**	1	-	**<.0001**	
		G2	1.48	0.78 to 2.83		1.45	0.75 to 2.80		
		G3	**5.83**	**2.86 to 11.92**		**5.65**	**2.71 to 11.76**		
		Stage: Ta, T1	**2.34**	**1.36 to 4.04**	**.022**	**2.15**	**1.23 to 3.77**	**.0076**	
		Associated TIS: no, yes	**1.86**	**1.09 to 3.19**	**.026**				
		Recurrence at 1st cystoscopy: no, yes	**5.22**	**3.51 to 7.78**	**<.0001**	**4.60**	**2.99 to 7.07**	**<.0001**	

Study (n patients)	Follow-up	Prognostic factor	Univariate analysis			Multivariate analysis			
			HR	95% CI	p-value	HR	95% CI	p-value	Factors adjusted for
Progression									
Palou 2012 N=146 T1G3	Median 104 months	Age(years): ≤65, >65 ≤60, 61-65, 66-70, >70	 1.89 1.33	 0.85 to 4.21 0.96 to 1.85	 .12 .09	 - -		 NS -	Age, number of tumours, tumour size, tumour aspect, CIS, and the combined variable "CIS in the prostatic urethra or female"
		Gender: male, female	2.41	0.96 to 6.04	.06	NA		-	
		Number of tumours: single, multiple	0.78	0.36 to 1.73	.54	-		NS	
		Size: ≤1.5cm, 1.5-3cm, >3cm	1.17	0.70 to 1.96	.54	-		NS	
		Tumour aspect: papillary, solid	1.52	0.67 to 3.43	.32	-		NS	
		T1 substage: T1a, T1b, T1c	1.43	0.88 to 2.32	.15	NA		-	
		Concomitant CIS: no, yes	1.46	0.61 to 3.49	.40	-		NS	
		CIS in prostatic urethra: no, yes	**4.35**	**1.65 to 11.50**	**.003**	NA		-	
		CIS in prostatic urethra: no, yes, female	-		**.002**	NA		-	
		CIS in prostatic urethra or female: no, yes	**3.59**	**1.64 to 7.88**	**.001**	**3.59**	**1.64 to 7.88**	**.001**	
Park 2009 N=144 T1G3	Median 52.5 months	Age: < median age, ≥median age			.874				
		Sex: male, female			.488				
		CIS: yes, no			.095				
		Multiplicity: single, multiple			.716	0.76	0.28 to 2.09	.594	

Study (n patients)	Follow-up	Prognostic factor	Univariate analysis			Multivariate analysis			
			HR	95% CI	p-value	HR	95% CI	p-value	Factors adjusted for
Progression									
		Size: <3cm, ≥3cm			.312	0.71	0.24 to 2.06	.528	
		Lymphovascular invasion: yes, no			.996				
		Gross morphology: papillary, non-papillary			**.031**				
		Microscopic morphology: papillary, non-papillary			**.0098**	**2.92**	**1.13 to 7.57**	**.027**	
		Intravesical therapy: no, yes			.098	0.61	0.22 to 1.74	.359	
		Proper muscle: absent, present			.341	1.55	0.54 to 4.41	.415	
Brimo 2013	Mean 29 months	Lymphovascular invasion: yes, no	1.55	0.34 to 7.01	.57	0.11	0.005 to 2.56	.171	
N=86		Adverse histological subtype: 'usual' UC, micropapillary/sarcomatoid UC	**15.7**	**3.87 to 63.97**	**.0001**	3.33	0.37 to 29.79	.282	
		Carcinoma in situ: yes, no	2.41	0.78 to 7.45	.13	1.78	0.49 to 6.44	.378	
		Maximum tumour diameter (mm)	**1.51**	**1.24 to 1.84**	**.0001**	**1.56**	**1.09 to 2.22**	**.014**	
Cho 2009	Median 35 mo, range	Lymphovascular invasion: yes, no	**3.27**	**1.32 to 8.11**	**.011**	**3.07**	**1.23 to 7.62**	**.016**	
N=118	12-89 mo	Gender: male, female	1.40	0.32 to 6.05	.655				
		Age: ≥65, <65	0.96	0.38 to 2.44	.933				
		Bladder tumour history: yes, no	1.54	0.51 to 4.33	.446				
		Size: ≥3cm, <3cm	2.54	1.0 to 6.46	.051	2.34	0.92 to 5.98	.075	

Study (n patients)	Follow-up	Prognostic factor	Univariate analysis			Multivariate analysis			
			HR	95% CI	p-value	HR	95% CI	p-value	Factors adjusted for
Progression									
		Number of tumours: ≥4, <4	1.51	0.60 to 3.77	.379				
		Grade: 3, 1&2	1.54	0.62 to 3.83	.355				
		Carcinoma in situ: yes, no	2.55	0.33 to 19.94	.373				
		Intravesical therapy: no, yes	1.67	0.55 to 5.05	.364				
Kwon 2012	Median 77 mo, range	Lymphovascular invasion: yes, no			**.023**	1.68	0.34 to 8.29	.525	
N=406	12-167 mo	Age				1.00	0.96 to 1.05	.834	
		Gender				1.00	0.47 to 2.50	.954	
		Stage: Ta, T1			**.013**	1.37	0.48 to 3.88	.559	
		Grade: low/high			**.002**	**2.57**	**1.48 to 4.46**	**.001**	
		Size: <3cm, ≥3cm				0.68	0.22 to 2.15	.512	
		Multiplicity: ≤3/>3			**.001**	0.55	0.25 to 1.21	.138	
Miyake 2011	Median 36 mo, range	Lymphovascular invasion: yes, no	**12.1**	**7.49 to 733.68**	**.0002**	1.23	0.13 to 11.28	0.86	
N=130	1-140 mo	Stage: Ta, T1	**20.69**	**7.82 to 446.23**	**<.0001**	**20.94**	**2.44 to 179.5**	**.006**	
		Grade (WHO 2004):PUNLMP/LG, HG	**14.37**	**3.25 to 126.40**	**.0013**	2.97	0.1 to 90.16	.53	
		Concomitant CIS: yes, no	ND		.51				
		Multiplicity: solitary, multiple	5.44	0.84 to 20.60	.082				
		Tumour diameter: <3cm, ≥3cm	**16.93**	**4.63 to 209.78**	**.0004**	6.77	0.69 to 66.8	.10	

Study (n patients)	Follow-up	Prognostic factor	Univariate analysis			Multivariate analysis			
			HR	95% CI	p-value	HR	95% CI	p-value	Factors adjusted for
Progression									
		Intravesical therapy: None, BCG	1.09	0.20 to 5.99	0.92				
Alkibay 2009 N=6 MPP+ N=125 MPP-	Median 27.2 months	Micropapillary pattern + versus Micropapillary pattern- *Odds ratio	5.14*	0.76 to 42.6	.064				
Olsson 2013 N=211	Median 60 months	Lymphovascular invasion no, yes	**3.00**	**1.55**	**5.71**	**2.92**	**1.47 to 5.81**	**0.002**	

Table 33. Univariate and multivariate analyses of overall survival

Study (n patients)	Follow-up	Prognostic factor	Univariate analysis			Multivariate analysis			
			HR	95% CI	p-value	HR	95% CI	p-value	Factors adjusted for
Overall survival									
Scosyrev 2009 N=104 SCC N=21462 UC	2-year cut-off	SCC vs. UC, with cystectomy SCC vs. UC, without cystectomy	-0.03* **0.20***	-0.16 to 0.11 **0.11 to 0.30**	.72 **<.001**				Age, grade, gender, race and radiotherapy
			*adjusted mortality difference						
Branchereau 2013 N=108	Mean 48 months	Lymphovascular invasion				NR	NR	**.003**	

Table 34. Univariate and multivariate analyses of disease-specific survival

Study (n patients)	Follow-up	Prognostic factor	Univariate analysis			Multivariate analysis			
			HR	95% CI	p-value	HR	95% CI	p-value	Factors adjusted for

Disease-specific survival									
Scosyrev 2009	2-year cut-off	SCC vs. UC, with cystectomy	-0.07[†]	-0.19 to 0.10	.64				Age, grade, gender, race and radiotherapy
N=104 SCC N=21462 UC		SCC vs. UC, without cystectomy	**0.17***	**0.08 to 0.26**	**<.001**				
			[†] unadjusted mortality difference *adjusted mortality difference						
Lopez 1995	Mean 47 mo, range	Vascular invasion: no, yes				**3.32**	**1.25 to 8.85**	**.016**	
N=170	18-86 mo	Tumour size: <5cm, >5cm				**7.80**	**3.33 to 18.31**	**.00001**	
		Growth pattern: papillary, flat				**4.50**	**1.67 to 12.13**	**.0031**	
		Grade (WHO 1973): I, II, III				1.74	0.60 to 5.10	.310	
Palou 2012	Median 104 months	Age(years): ≤65, >65	2.47	0.92 to 6.58	.07	-		NS	Age, number of tumours, tumour size, tumour aspect, CIS, and the combined variable "CIS in the prostatic urethra or female"
N=146 T1G3		≤60, 61-65, 66-70, >70	**1.56**	**1.04 to 2.35**	**.03**	-		-	
		Gender: male, female	1.87	0.61 to 5.69	.27	NA		-	
		Number of tumours: single, multiple	0.84	0.33 to 2.13	.72	-		NS	
		Size: ≤1.5cm, 1.5-3cm, >3cm	1.36	0.73 to 2.53	.34	-		NS	
		Tumour aspect: papillary, solid	1.38	0.52 to 3.68	.52	-		NS	
		T1 substage: T1a, T1b, T1c	1.22	0.69 to 2.13	.50	NA		-	
		Concomitant CIS: no, yes	1.13	0.42 to 3.00	.81	-		NS	
		CIS in prostatic urethra: no, yes	**5.14**	**1.71 to 15.45**	**.004**	NA		-	
		CIS in prostatic urethra: no, yes, female	**-**		**.006**	NA		-	

Study (n patients)	Follow-up	Prognostic factor	Univariate analysis			Multivariate analysis			
			HR	95% CI	p-value	HR	95% CI	p-value	Factors adjusted for
Disease-specific survival									
		CIS in prostatic urethra or female: no, yes	**3.53**	**1.40 to 8.89**	**.004**	**3.53**	**1.40 to 8.89**	**.004**	
Tilki 2012 N=101		Lymphovascular invasion no, yes			**.004**	**6.7**	**1.5 to 30.3**	**0.01**	
Olsson 2013 N=211	Median 60 months	Lymphovascular invasion no, yes	1.88	0.85 to 4.17		1.56	0.67 to 3.64	0.36	

Table 35. Validation studies of the EORTC risk tables

Concordance index (c-index) used to asses model accuracy. It represents the probability of concordance between the predicted and observed outcomes. A c-index of 0.50 represents agreement by chance. Perfect discrimination corresponds to a c statistic of 1 and is achieved if the scores for all the cases are higher than those for all the non-cases, with no overlap. Note that the c-index is not the probability that individuals are classified correctly.

Study	**C-index at 1 year**		**C-index at 5 years**	
	Recurrence	Progression	Recurrence	Progression
EORTC (Sylvester 2006)	0.66	0.74	0.66	0.75
CUETO (Fernandez-Gomez 2011)	0.63	0.69	0.63	0.68
Xylinas 2013			0.597	0.662

Table 36. Validation studies of the EORTC risk tables

Prognostic separation index (PSEP) ($P_{worst} – P_{best}$) is based on the difference between the P_{worst} (the predicted probability of recurrence or progression in the group with the poorest prognosis) and P_{best} (the corresponding value for those of the best prognosis group). The greater the difference or separation between these two values, the better the PSEP and the more useful the test for discriminating between individuals with good and poor prognoses.

Study	**PSEP at 1 year**			**PSEP at 5 years**		
	Recurrence (1)*	Recurrence (2)*	Progression	Recurrence (1)*	Recurrence (2)*	Progression
EORTC (Sylvester 2006)	0.46		0.168	0.47		0.42
CUETO (Fernandez-Gomez 2011)	0.3	0.26	0.105	0.49	0.51	0.25

* Recurrence (1): All recurrent tumours were considered as having no more than one recurrence per year. Recurrence (2): All tumours were considered as having more than one recurrence per year.

Table 37. Probabilities of recurrence according to EORTC risk tables and validation studies at 1-year and 5-year

EAU guideline risk group	EORTC Recurrence prediction 1-year (95% CI)	Van Rhijn 2010	Seo 2010 (n/N)	CUETO cohort (95% CI)	Hernandez 2011 (95% CI)	Altieri 2012	Xu 2013 (95% CI)	Lammers 2014 95% CI
Low risk	15% risk (10%-19%)	29%*	0% (0/1)	0%	5.9% (2.5-13.6)	7.9%	9% (3-15)	0
Intermediate risk	24% risk (21%-26%)	50%*	9.2% (7/76)	8% (7.4-8.7)	22.4% (17.2-28.9)	20.5%	16% (10-22)	16-21
	38% risk (35%-41%)		37.9% (47/124)	15.2% (14.6-16.4)	42.8% (34.4-52.3)	25%	32% (24-40)	27-31
High risk	61% risk (55%-67%)	-	50% (25/50)	30.28% (27.2-36.5)	50% (19.6-88.9)	41.2%	80 (55-100)	41-54
	EORTC Recurrence prediction 5-year (95% CI)	**Van Rhijn 2010**	**Seo 2010 (n/N)**	**CUETO cohort (95% CI)**	**Hernandez 2011 (95% CI)**	**Altieri 2012**	**Xu 2013 (95% CI)**	**Lammers 2014 95% CI**
Low risk	31% risk (24%-37%)	52%	0% (0/1)	0%	27.9% (18.4-40.9)	18.4%	27% (15-39)	0
Intermediate risk	46% risk (42%-49%)	71%	13.2% (10/76)	23% (21.7-26.2)	54.9% (47.3-63)	32.2%	44% (34-54)	44-55
	62% risk (58%-65%)		46.8% (58/124)	34.1% (32.5-37.5)	66.8% (57.2-76.2)	44.6%	67% (57-77)	66-71
High risk	78% risk (73%-84%)	-	72% (36/50)	49.1% (43.5-60.6)	50% (19.6-88.9)	52.9%	80% (55-100)	0

*2 year recurrence rate

Table 38. Probabilities of progression according to EORTC risk tables and validation studies at 1-year and 5-year

EAU guideline risk group	EORTC progression prediction 1-year (95% CI)	Van Rhijn 2010	Seo 2010 (n/N)	CUETO cohort (95% CI)	Hernandez 2011 (95% CI)	Altieri 2012	Xu 2013	Lammers 2014 95% CI
Low risk	0.2% risk (0%-0.7%)		0% (0/5)	0%	1.4% (0.2-9.8)	0%	0% (0-0)	0
Intermediate risk	1% risk (0.4%-1.6%)		1.8% (1/57)	1% (0.91	3.0% (1.4-6.6)	2.5%	1% (0-3)	0.8-2
High risk	5% risk (4%-7%)		7.8% (12/154)	3.9% (3.6-4.2)	7.9% (4.4-14.3)	4.7%	7% (1.1-13)	3-7
	17% risk (10%-24%)		11.4% (4/35)	10.5% (8.7-12.4)	21.2% (7.3-52)	17.4%	27% (5-49)	0
EAU guideline risk group	**EORTC progression prediction 5-year (95% CI)**	**Van Rhijn 2010**	**Seo 2010 (n/N)**	**CUETO cohort (95% CI)**	**Hernandez 2011 (95% CI)**	**Altieri 2012**	**Xu 2013 (95% CI)**	**Lammers 2014 95% CI**
Low risk	0.8% risk (0%-1.7%)	2%	0% (0/5)	0%	1.4% (0.2-9.8)	1.9%	0% (0-0)	0
Intermediate risk	6% risk (5%-8%)	10%	3.5% (2/57)	4.8% (4.2-5.5)	6.2% (3.5-11.1)	7.5%	4% (0.1-8)	0
High risk	17% risk (14%-20%)	25%	20.8% (32/154)	14.1% (12.7-15.6)	14.1% (8.8-22.2)	12.5%	21 % (9-33)	0
	45% risk (35%-55%)		34.3% (12/35)	25.6% (20-31.3)	21.2% (7.3-52.7)	39.1%	48% (18-78)	0

Figure 31. Univariate analyses of lymphovascular invasion on recurrence

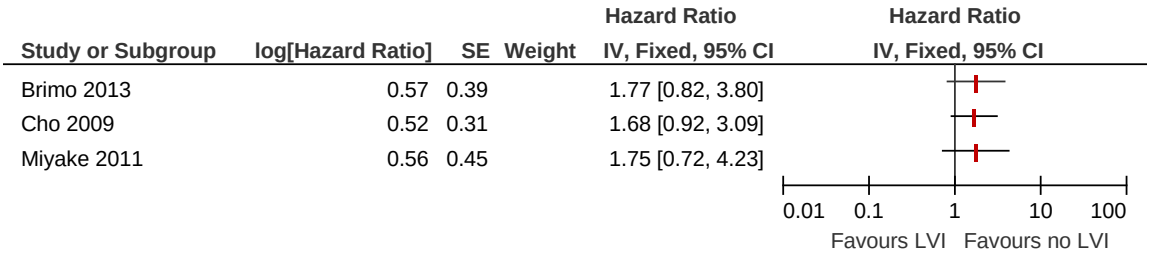


Figure 32. Multivariate analyses of lymphovascular invasion on recurrence

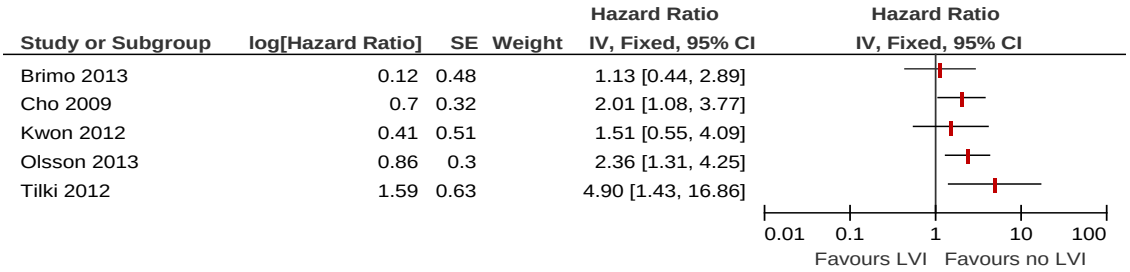


Figure 33. Univariate analyses of lymphovascular invasion on progression

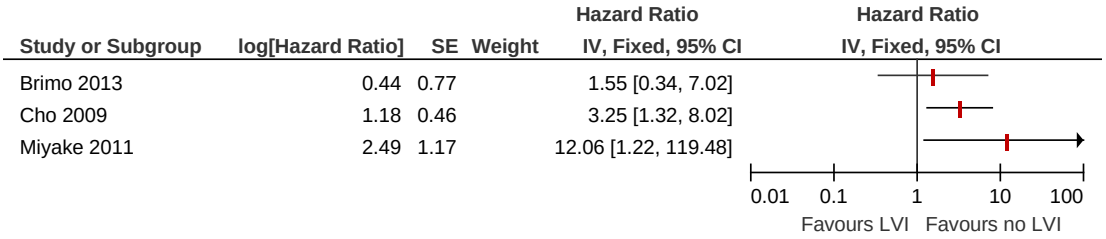


Figure 34. Multivariate analyses of lymphovascular invasion on progression

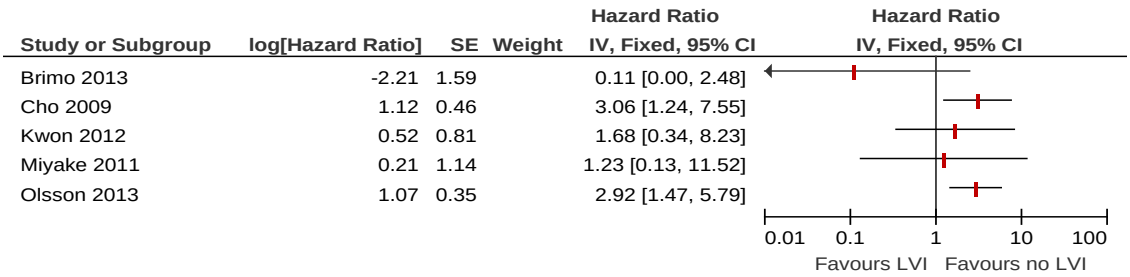
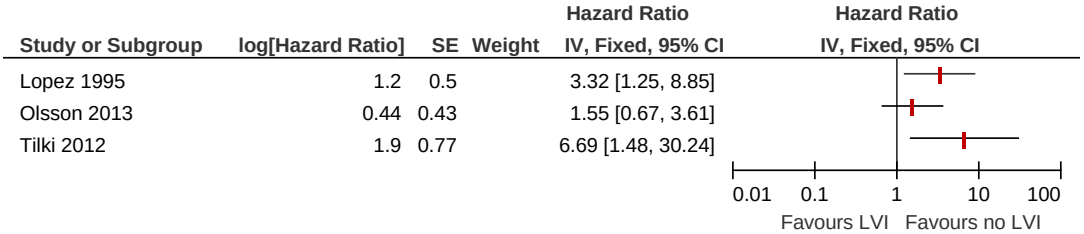


Figure 35. Multivariate analyses of lymphovascular invasion on disease-specific survival



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Branchereau, J et al. Prognostic value of the lymphovascular invasion in high-grade stage pT1 bladder cancer. Clinical Genitourinary Cancer 2013; 11(2): 182-188.

Brimo, F et al. Prognostic factors in T1 bladder urothelial carcinoma: the value of recording millimetric depth of invasion, diameter of invasive carcinoma, and muscularis mucosa invasion. Human Pathology 2013; 44(1): 95-102.

Cho, KS et al. Lymphovascular invasion in transurethral resection specimens as predictor of progression and metastasis in patients with newly diagnosed T1 bladder urothelial cancer. Journal of Urology 2009; 182(6): 2625-2630.

Fernandez-Gomez, J et al. Prognostic factors in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin: Multivariate analysis of data from four randomized CUETO trials. European Urology 2008; 53(5): 992-1002.

Fernandez-Gomez, J et al. The EORTC tables overestimate the risk of recurrence and progression in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin: external validation of the EORTC risk tables. European Urology 2011; 60(3): 423-430.

Hernandez, V et al. External validation and applicability of the EORTC risk tables for non-muscle-invasive bladder cancer. World Journal of Urology 2011; 29(4): 409-414.

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Miyake, M et al. Clinical significance of subepithelial growth patterns in non-muscle invasive bladder cancer. BMC Urology 2011; 11(1): 17

Olsson, H et al. Population-based study on prognostic factors for recurrence and progression in primary stage T1 bladder tumours. Scandinavian Journal of Urology 2013; 47(3): 188-195.

Palou, J et al. Female Gender and Carcinoma In Situ in the Prostatic Urethra Are Prognostic Factors for Recurrence, Progression, and Disease-Specific Mortality in T1G3 Bladder Cancer Patients Treated With Bacillus Calmette-Guerin. European Urology 2012; 62(1): 118-125.

Park, J et al. Prognostic significance of non-papillary tumor morphology as a predictor of cancer progression and survival in patients with primary T1G3 bladder cancer. World Journal of Urology 2009; 27(2): 277-283.

Sakano, S et al. Risk group stratification to predict recurrence after transurethral resection in Japanese patients with stage Ta and T1 bladder tumours: validation study on the European Association of Urology guidelines. BJU International 2011; 107(10): 1598-1604.

Scosyrev, E, Yao, J, and Messing, E. Urothelial carcinoma versus squamous cell carcinoma of bladder: is survival different with stage adjustment? Urology 2009; 73(4): 822-827.

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Sylvester, RJ et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. European Urology 2006; 49(3): 466-475.

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van Rhijn, BW et al. Prognostic value of molecular markers, sub-stage and European Organisation for the Research and Treatment of Cancer risk scores in primary T1 bladder cancer. BJU International 2012; 110(8): 1169-1176.

Xu, T et al. Predicting recurrence and progression in Chinese patients with nonmuscle-invasive bladder cancer using EORTC and CUETO scoring models. Urology 2013; 82(2): 387-393.

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Reason: not relevant to PICO (MIBC)

Jeon, SH, Jeon, SH, and Chang, SG. Clinical prognostic factors for radical cystectomy in bladder cancer. Cancer Research & Treatment 2005; 37(1): 48-53.

Reason: population not relevant to PICO (RC cohort)

Samaratunga, H and Khoo, K. Micropapillary variant of urothelial carcinoma of the urinary bladder; a clinicopathological and immunohistochemical study. Histopathology 2004; 45(1): 55-64.

Reason: not study of prognosis

Pich, A et al. Proliferative activity is the most significant predictor of recurrence in noninvasive papillary urothelial neoplasms of low malignant potential and grade 1 papillary carcinomas of the bladder. Cancer 2002; 95(4): 784-790.

Reason: prognostic factors not in PICO

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Reason: expert review

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Reason: expert review

van den Bosch, S and Alfred, WJ. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. [Review]. European Urology 2011; 60(3): 493-500.

Reason: not a prognostic study

Herrmann, E et al. The prognostic impact of pelvic lymph node metastasis and lymphovascular invasion on bladder cancer. International Journal of Urology 2008; 15(7): 607-611.

Reason: population not relevant to PICO (MIBC)

Kim, SP et al. The impact of squamous and glandular differentiation on survival after radical cystectomy for urothelial carcinoma. Journal of Urology 2012; 188(2): 405-409.

Reason: population not relevant to PICO (RC cohort)

Ehdaie, B et al. Comparative outcomes of pure squamous cell carcinoma and urothelial carcinoma with squamous differentiation in patients treated with radical cystectomy. Journal of Urology 2012; 187(1): 74-79.

Reason: population not relevant to PICO (RC cohort)

Abdollah, F et al. Survival after radical cystectomy of non-bilharzial squamous cell carcinoma vs. urothelial carcinoma: a competing-risks analysis. BJU International 2012; 109(4): 564-569.

Reason: population not relevant to PICO (RC cohort)

Rodriguez, FO et al. Clinical predictive factors of poor outcome in patients with stage pT0 disease at radical cystectomy. Journal of Urology 2011; 186(2): 442-447.

Reason: population not relevant to PICO (RC cohort)

Resnick, MJ et al. Longitudinal evaluation of the concordance and prognostic value of lymphovascular invasion in transurethral resection and radical cystectomy specimens. BJU International 2011; 107(1): 46-52.

Reason: population not relevant to PICO (MIBC and NMIBC not reported separately)

Wasco, MJ et al. Urothelial carcinoma with divergent histologic differentiation (mixed histologic features) predicts the presence of locally advanced bladder cancer when detected at transurethral resection. Urology 2007; 70(1): 69-74.

Reason: population not relevant to PICO (MIBC)

Wang, J et al. Clinical features of sarcomatoid carcinoma (carcinosarcoma) of the urinary bladder: analysis of 221 cases. Sarcoma 2010; 2010, 2010.

Reason: not relevant to PICO (not prognostic study)

Shariat, SF et al. International validation of the prognostic value of lymphovascular invasion in patients treated with radical cystectomy. BJU International 2010; 105(10): 1402-1412.

Reason: population not relevant to PICO (MIBC, RC cohort)

Ploeg, M et al. Clinical epidemiology of nonurothelial bladder cancer: analysis of the Netherlands Cancer Registry. Journal of Urology 2010; 183(3): 915-920.

Reason: population not relevant to PICO (MIBC)

Bolenz, C et al. Lymphovascular invasion is an independent predictor of oncological outcomes in patients with lymph node-negative urothelial bladder cancer treated by radical cystectomy: a multicentre validation trial. BJU International 2010; 106(4): 493-499.

Reason: population not relevant to PICO (MIBC)

Chang, WC, Chang, YH, and Pan, CC. Prognostic significance in substaging ofT1 urinary bladder urothelial carcinoma on transurethral resection. American Journal of Surgical Pathology 2012; 36(3): 454-461.

Reason: prognostic factors not relevant to PICO

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Reason: not prognostic study

Rogers, CG et al. Clinical outcomes following radical cystectomy for primary nontransitional cell carcinoma of the bladder compared to transitional cell carcinoma of the bladder. Journal of Urology 2006; 175(6): 2048-2053.

Reason: RC cohort, NMIBC and MIBC not reported separately

Wasco, MJ et al. Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases. Human Pathology 2010; 41(2): 163-171.

Reason: population not relevant to PICO (MIBC)

Wright, JL et al. Differences in survival among patients with sarcomatoid carcinoma, carcinosarcoma and urothelial carcinoma of the bladder. Journal of Urology 2007; 178(6): 2302-2306.

Reason: population not relevant to PICO (MIBC and NMIBC not reported separately)

Pillai, R, Wang, D, and Abel, P. Is the proposed EORTC prognostic algorithm for pTa/pT1 bladder transitional cell cancer (TCC) valid in a routine clinical setting? European Urology Supplements 2007; 6(2): 172-172.

Reason: duplicate, abstract only

Streeper, NM et al. The significance of lymphovascular invasion in transurethral resection of bladder tumour and cystectomy specimens on the survival of patients with urothelial bladder cancer. BJU International 2009; 103(4): 475-479.

Reason: population not relevant to PICO (stage 1+2 reported together)

May, M et al. Pathological upstaging detected in radical cystectomy procedures is associated with a significantly worse tumour-specific survival rate for patients with clinical T1 urothelial carcinoma of the urinary bladder. Scandinavian Journal of Urology & Nephrology 2011; 45(4): 251-257.

Reason: population not relevant (T2 and RC cohort)

Tilki, D et al. Characteristics and outcomes of patients with clinical carcinoma in situ only treated with radical cystectomy: an international study of 243 patients. Journal of Urology 2010; 183(5): 1757-1763.

Reason: population not relevant (CIS refractory to BCG only, RC cohort)

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Reason: outcomes not relevant to PICO

Rosevear, HM. Usefulness of the Spanish Urological Club for Oncological Treatment scoring model to predict nonmuscle invasive bladder cancer recurrence in patients treated with intravesical bacillus Calmette-Guerin plus interferon-alpha. Journal of Urology 2011; 185(1): 67-71.

Reason: not relevant to PICO (CUETO prognostic factors)

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Reason: not relevant to PICO (RC cohort, includes MIBC)

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Reason: not prognostic study / mostly MIBC

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Reason: not relevant to PICO (mostly MIBC)

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Reason: prognostic factor not relevant to PICO

Pillai, R et al. Do standardised prognostic algorithms reflect local practice? Application of EORTC risk tables for non-muscle invasive (pTa/pT1) bladder cancer recurrence and progression in a local cohort. Thescientificworldjournal 2011; 11: 751-759.

Reason: insufficient validation cohort, no patients in some groups

Ather, MH and Zaidi, M. Predicting recurrence and progression in non-muscle-invasive bladder cancer using European organization of research and treatment of cancer risk tables. Urology Journal 2009; 6(3): 189-193.

Reason: insufficient validation cohort, no patients in some risk groups

Alkhateeb, SS et al. Long-term prognostic value of the combination of EORTC risk group calculator and molecular markers in non-muscle-invasive bladder cancer patients treated with intravesical Bacille Calmette-Guerin. Urology annals 2011; 3(3): 119-126.

Reason: insufficient validation cohort, no patients in some risk groups

Sylvester, R et al. Prognostic factors in patients with intermediate and high risk stage Ta T1 papillary carcinoma of the bladder treated with maintenance epirubicin or maintenance bacillus Calmette-Guerin. Results of EORTC GU group study 30911. Journal of Urology 2008; 179(4): 586-586.

Reason: abstract only, insufficient information for inclusion

Wang, JK et al. Outcomes following radical cystectomy for micropapillary bladder cancer versus pure urothelial carcinoma: a matched cohort analysis. World Journal of Urology 2012; 30(6): 801-806.

Reason: population not relevant to PICO (MIBC)

Rodriguez, FO and Palou, J. Predictive factors for recurrence progression and cancer specific survival in high-risk bladder cancer. [Review]. Current Opinion in Urology 2012; 22(5): 415-420.

Reason: expert review

Yamazaki, K, Kumamoto, Y, and Tsukamoto, T. Expression of squamous cell carcinoma-associated antigen in grade 3 pT1 transitional cell carcinoma of the bladder and prediction of its progression and intravesical recurrence. Cancer 1993; 72(12): 3676-3684.

Reason: prognostic factor not relevant to PICO, no SCC component in carcinoma

Van Der Aa, MNM. Clinical and pathological prognostic factors for recurrence, progression and mortality in non-muscle invasive bladder cancer: A meta-analysis. Current Urology 2009; 3(3): 113-123.

Reason: prognostic factors not relevant to PICO

Pan, CC et al. Constructing prognostic model incorporating the 2004 WHO/ISUP classification for patients with non-muscle-invasive urothelial tumours of the urinary bladder. Journal of Clinical Pathology 2010; 63(10): 910-915.

Reason: prognostic factors not relevant to PICO

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Reason: abstract only

Kohjimoto, Y. External validation of eortc and cueto scoring models to predict recurrence and progression in patients with nonmuscle invasive bladder cancer treated with bacillus calmette-guerin. Journal of Urology 2012; 187(4): E716-E717.

Reason: abstract only

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Reason: insufficient validation study

Borkowska, EM et al. EORTC risk tables - their usefulness in the assessment of recurrence and progression risk in non-muscle-invasive bladder cancer in Polish patients. Central European Journal of Urology 2013; 66(1): 14-20.

Reason: insufficient validation study

Walczak, R, Bar, K, and Walczak, J. The value of EORTC risk tables in evaluating recurrent non-muscle-invasive bladder cancer in everyday practice. Central European Journal of Urology 2014; 66(4): 418-422.

Reason: insufficient data for inclusion – outcomes reported not relevant to PICO

Evidence tables

Study	N patients	Patient Characteristics		Follow-up	Outcomes	Prognostic factors	Comments
Sylvester 2006	2596 (from 7 EORTC randomised trials comparing prophylactic treatments after TUR) Median age =65 years 79% M / 20% F / 1% unknown	Intravesical treatment		Median 3.9 years, maximum 14.8 years	Time to first recurrence Time to progression	Age Gender Prior treatment Prior recurrence rate No. of tumours Tumour size T category Presence of CIS Grade T1G3 Recurrence at 3 months	
		No	561 (21.6)				
		Yes	2035 (78.4)				
		Prior treatment					
		No	2358 (90.8)				
		Yes	187 (7.2)				
		Prior recurrence rate					
		Primary	1405 (54.1)				
		Recurrent ≤1 rec/yr	505 (19.5)				
		Recurrent >1 rec/yr	645 (24.8)				
		N tumours					
		1	1405 (54.1)				
		2-7	836 (32.2)				
		≥8	255 (9.8)				
		Tumour size					
		<1cm	920 (53.4)				
		<3cm	1167 (45)				
		≥3cm	464 (17.9)				
		T category					
		Ta	1451 (55.9)				
		T1	1108 (42.7)				
		Carcinoma in situ					
		No	2440 (94)				
		Yes	113 (4.4)				
		Grade					
		G1	1121 (43.2)				
		G2	1139 (43.9)				

Study	N patients	Patient Characteristics		Follow-up	Outcomes	Prognostic factors	Comments
		G3	271 (10.4)				
		T1G3					
		No	2361 (90.9)				
		Yes, No CIS	172 (6.6)				
		Yes, with CIS	22 (0.8)				
		Recurrence at 3 months					
		No	2070 (79.7)				
		Yes	313 (12.1)				
		Recurrence					
		No	1356 (52.2)				
		Yes	1240 (47.8)				
		Progression					
		No	2317 (89)				
		Yes	279 (10.7)				
		Survival					
		Alive	1743 (67.1)				
		Dead	853 (32.9)				
Fernandez-Gomez 2008	N=1062 (from 4 randomised trials of intravesical therapy) Median age 66 yrs 90% M / 10% F All received BCG, Connaught strain, weekly for 6 wks, then every 2 wks x6. 33% had recurrence, 13% progressed into MIBC	T category n(%)		Median 69 mo	Recurrence Progression (to stage T2 or higher)	Age Primary vs. recurrent tumour No. and size of tumour Doses of BCG and no. of instillations T category Grade Presence of CIS Recurrence at 1st cystoscopy	
		Ta	214 (20.2)				
		T1	848 (79.8)				
		Recurrent tumour					
		No	706 (66.5)				
		Yes	356 (33.5				
		Grade					
		G1	167 (15.7)				
		G2	629 (59.2)				
		G3	266 (25)				
		No. of tumours					
		1	535 (50.4)				
		2-3	278 (26.2)				
		4-7	160 (15.1)				
		≥8	89 (8.4)				

Study	N patients	Patient Characteristics	Follow-up	Outcomes	Prognostic factors	Comments
		Tumour size ≤1 cm 283 (26.6) 1-3 cm 298 (28.1) ≥3cm 481 (45.3) Concomitant CIS No 982 (92.5) Yes 80 (7.5) No. of instillations <6 45 (4.2) 6-9 239 (22.5) ≥10 778 (73.5) Doses 13.5mg 137 (12.9) 27mg 434 (40.9) 81mg 491 (46.2)				
Miyake 2011 Japan	N=130 88% M/12% F Newly diagnosed NMIBC 1998-2009. 75/130 (58%) received adjuvant therapy after TURBT: 67 BCG, 8 epirubicin.	T category n(%) Ta 104 (80) T1 26 (20) Grade WHO 2004 PUNLMP 13 (10) LG 84 (65) HG 33 (25) Concomitant CIS No 123 (95) Yes 7 (5) Lymphovascular involvement No 110 (85) Yes 20 (15) Multiplicity Solitary 70 (54) multiple 60 (46) Tumour diameter <3 99 (76) ≥3 31 (24)	Median 36 mo (range 1-140 mo)	Progression (to muscle invasive disease, or a metastatic site in other organs) Recurrence (after resection)	T stage Tumour grade CIS Lymphovascular involvement Endophytic growth pattern Von Brunn's nest involvement Multiplicity Tumour diameter (cm) Intravesical therapy	
Kwon 2012 Korea	N=406 Mean age 64.4±11.4	T category n(%) Ta 274 (67.5)	Median 76.9 mo (range 12-167 mo)	Recurrence Progression (shift to stage ≥T2)	Age Gender Underlying diseases	

Study	N patients	Patient Characteristics	Follow-up	Outcomes	Prognostic factors	Comments
	years 84% M / 17% F Patients with NMIBC who underwent TURBT 1999-2010. Must have tumour resection weight available. Excluded: CIS, no BCG, evidence of metastases One immediate intravesical chemo done among the included patients	T1 132 (32.5) Grade WHO 2004 Low 165 (41) High 241 (59.4) Tumour weight ≥2 241 (59) <2 165 (41) Lymphovascular involvement No 394 (97) Yes 12 (3) No. of tumours 1-3 103 (25) >3 303 (75) Tumour size (cm) ≥3 192 (47) <3 214 (53)			Cancer stage Grade Multiplicity Size Lymphovascular invasion Resection weight	
Cho 2009 Korea	N=118 Median age 67 (range 39-91) years 86% M / 14% F Newly diagnosed T1 bladder UC. Repeat TURBT 31 (26%), 100 (85%) intravesical therapy: 65 MMC, 27 BCG (6-wk), 8 epirubicin. Systemic chemo recommended in patients with multifocal LVI. 11 patients had 2-3 cycles of cisplatin based chemo. 4 patient had RC	Tumour Grade n(%) 1 3 (2.5) 2 60 (50.8) 3 55 (46.6) CIS No 113 (95.8) Yes 5 (4.2) Lymphovascular involvement No 85 (72) Yes 33 (28) No. of tumours <4 57 (48) ≥4 61 (52) Tumour size (cm) <3 70 (59) ≥3 48 (41) Repeat TURBT No 87 (74) Yes 31 (26) Intravesical therapy	Median 35 mo (range 12-89)	Recurrence Progression (muscularis propria invasion by UC and/or new onset metastatic disease.	Lymphovascular invasion (considered present only when tumour cells were unequivocally noted within or attached to the wall of a vascular or lymphatic space on hematoxylin and eosin stained sections) Gender Age Bladder tumour history Tumour size No. Tumours Tumour grade CIS Repeat TUR Intravesical therapy Systemic therapy	

Study	N patients	Patient Characteristics	Follow-up	Outcomes	Prognostic factors	Comments
		No 18 (15) Yes 100 (85) Recurrence No 73 (62) Yes 45 (38) Progression No 99 (84) Yes 19 (16)				
Brimo 2013 Canada	N=86 Mean age 71 years Patients with pT1 and treated with TURBT 2004-2012	All urothelial carcinoma except 3 mircopapillary and 1 sarcomatoid. 13% lymhovascular invasion. None had history of invasive UC. Repeat TUR not routinely performed if there was adequate muscularis propria in the specimen and was left to discretion of urologist.	Mean 29 months	Recurrence (any subsequent lesion including CIS and noninvasive papillary neoplasms) Progression (pT2 in subsequent TURB specimens)	Muscularis mucosa invasion Millimetric depth of invasion Total diameter of invasive carcinoma No of fragments containing invasion Lymphovascular invasion (considered present only if it was unequivocally present on hematoxylin and eosin sections) Concomitant CIS Histological subtype	Unclear whether patients received adjuvant intravesical therapy
Scosyrev 2009 USA	N=1422 patients with pure squamous cell carcinoma N=107613 urothelial carcinomas for comparison	85% of SCCs were muscle invasive. 22% of UCs were muscle invasive. SCC Stage 1 n=104, UC Stage 1 n=21462. Mean age SCC =74 yrs, UC=72 yrs Women (%) SCC=54, UC=23 High grade (%) SCC=39, UC=59 Cystectomy (%) SCC =17.3, UC=6.1 Radiotherapy (%) SCC=10.6, UC =1.9	2 years	All-cause mortality Bladder cancer specific mortality	Histologic type (UC vs. pure SCC) Age Gender Race AJCC stage Grade (well/moderately/poorly differentiated, undifferentiated) Treatment (cystectomy, radiotherapy)	Modified least squares model with identity link function and robust variance estimator used rather than Cox model
Lopez 1995 Spain	N=170 T1 bladder tumours undergoing TUR	17/170 (10%) displayed unequivocal vascular invasion. 15 Male, 2 female. Aged between 60-71 (mean age 69.5)	Mean 47 mo, range 18-86 mo	Overall survival	Lymphovascular invasion (H&E staining, present when tumour cells were unequivocally noted within or	

Study	N patients	Patient Characteristics	Follow-up	Outcomes	Prognostic factors	Comments
	followed by long term instillations of either MMC or adriamycin.	Vascular invasion was confined to the lamina propria in 16 cases, and extended into the level of muscularis propria in one case.			attached to the wall of a vascular or lymphatic space. All positive cases verified using immunohistochemistry) Grade Presence of papillary phenotype Tumour size	
Palou 2012	N=146 Mean age 64.9 years (range 25-81) 88% M / 12% F All T1G3 (1985-1996) underwent complete TUR with muscle in specimen. No second TURBT. One induction course of BCG (81mg, Connaught) without maintenance treatment. 65 (44.5%) have recurrence 25 (17.1%) have progressed 56 (38.4%) died 18 (12.3%) died from BCa	Substage n(%) T1a 48 (32.9) T1b 23 (15.7) T1c 22 (15.1) T1x 53 (36.3) Tumour diameter (cm) <1.5 42 (28.8) 1.5-3 63 (43.1) >3 41 (28.1) Concomitant CIS Yes 95 (65.1) No 51 (34.9) CIS in prostatic urethra Yes 15 (10.3) No 131 (89.7) Multifocal disease Yes 74 (50.7) No 72 (49.3) Tumour aspect Papillary 105 (71.9) Solid 41 (28.1) Female or prostatic urethra Yes 33 (22.6) No 111 (76) Unknown 2 (1.4)	Median 8.7 years, maximum 13.9 years	Recurrence Progression (≥T2 or metastatic disease) Cancer-specific survival	Age Gender Multiplicity (single or multiple) Largest diameter (<1.5cm, 1.5-3cm, >3cm) Tumour aspect (Papillary or solid) Substage (T1a,T1b, T1c) Concomitant CIS CIS in prostatic urethra	
Van Rhijn 2010	N=230 Mean age 65.1±12.3 yr 76% M/ 24% F	Stage n(%) Ta 171(74) T1 59 (26) Tumour diameter	Median 8.62 years, IQR 6.6-11.8 yrs.	Recurrence Progression Disease-specific survival	Gender Age Hospital Stage Grade	Validation of EORTC risk groups

Study	N patients	Patient Characteristics		Follow-up	Outcomes	Prognostic factors	Comments
		≤3cm	140 (61)			CIS Size Multiplicity EORTC recurrence Molecular grade FGFR3	
		>3	90 (39)				
		Concomitant CIS					
		Yes	12 (5)				
		No	218 (95)				
		Multiplicity					
		Solitary	165 (72)				
		Multiple	65 (28)				
		Grade (WHO 1973)					
		G1	88 (38)				
		G2	108 (47)				
		G3	34 (15)				
		Grade (WHO 2004)					
		PUNLMP	82 (36)				
		LG	80 (35)				
		HG	68 (29)				
		EORTC recurrence					
		Low risk	54 (24)				
		Intermediate	176 (76)				
		EORTC progression					
		Low	80 (35)				
		Intermediate	91 (39)				
		High	59 (26)				
		Instillation type					
		None	72 (31)				
		Chemotherapy	58 (25)				
		BCG	58 (25)				
		BCG + chemo	42 (19)				
		No. of instillations					
		0	72 (31)				
		4-6	30 (13)				
		7-12	25 (11)				
		13-18	31 (14)				
		>18	72 (31)				
Van Rhijn 2012 1984-2006	N=129 Mean (SD) age 68.8 (9.9)	Sub-stage n(%)		Median 6.5 years	Recurrence Progression (≥pT2 and/or metastases)	Size Multiplicity Hospital Gender	
		T1a	79 (61)				
		T1b	17 (13)				

Study	N patients	Patient Characteristics	Follow-up	Outcomes	Prognostic factors	Comments
Netherlands	81% M / 19% F All T1. All patients had induction BCG. No single instillation or random biopsies	T1c: 33 (26) Tumour size ≤3cm: 67 (52) >3: 62 (48) Concomitant CIS No: 84 (65) Yes: 45 (35) Multiplicity Solitary: 77 (60) Multiple (2-7): 52 (40) Grade (WHO 1973) G2: 55 (43) G3: 74 (57) Grade (WHO 2004) LG: 26 (20) HG: 103 (80) EORTC recurrence Intermediate: 122 (95) High risk: 7 (5) EORTC progression Intermediate: 16 (12) High: 113 (88) Instillation type BCG: 106 (82) BCG + chemo: 23 (18) No. of instillations 4-6: 32 (25) 7-12: 32 (25) 13-18: 26 (20) >18: 39 (30)			Age CIS Grade (WHO 2004/1973) EORTC recurrence and progression T1 Sub-stage Molecular markers (FGFR3, Ki-67, P27)	
Seo 2010 Korea 1993-2007	N=251 57% ≤65 years 43% >65 years 76% M / 24% F All received BCG	Stage n(%) Ta: 44 (20.1) T1: 175 (79.9) Tumour diameter <3cm: 155 (61.8) ≥3: 96 (38.2) CIS	Mean 68.9 months, range 12-204 months	Recurrence Progression	NA Recurrence and progression rates were compared with the values presented in the EORTC tables.	

Study	N patients	Patient Characteristics		Follow-up	Outcomes	Prognostic factors	Comments
	(Oncotice) for 6 weeks then 1x/month for 3 months	No	213 (84.9)				
		Yes	38 (15.1)				
		No. of tumours					
		1	62 (24.7)				
		2-7	109 (43.4)				
		≥8	80 (31.9)				
		Grade (WHO 1973)					
		G1	61 (24.3)				
		G2	124 (49.4)				
		G3	66 (26.3)				
		Prior recurrence rate					
		Primary	224 (89.2)				
		≤1 rec/year	16 (6.4)				
		>1 rec/year	11 (4.4)				
Sakano 2010 Japan 2004-2006	N=592 (372 classified into EORTC risk groups) Median age 73 (33-95) 79% M / 20% F Primary CIS and patients with systemic chemo or radiotherapy or cystectomy after TUR excluded 189 (32%) received intravesical chemo, 92 (15.5%) BCG. No maintenance BCG	Stage n(%)		Median 37 months, range 3-69	Recurrence	Age ECOG PS Prior recurrence rate No. of tumours T category Grade Gender Tumour size Concomitant CIS Histopathology Intravesical therapy Recurrence-free survival curves were also plotted for the EORTC risk groups	
		Ta	287 (48.5)				
		T1	305 (51.5)				
		Tumour size					
		≤3cm	562 (94.9)				
		> 3cm	25 (4.2)				
		Concomitant CIS					
		No	360 (60.8)				
		Yes	53 (9.0)				
		Unknown	179 (30.2)				
		No. of tumours					
		1	304 (51.5)				
		2-7	264 (44.6)				
		≥8	22 (3.7)				
		Grade (WHO 1973)					
		G1	105 (17.7)				
		G2	334 (56.4)				
		G3	145 (24.5)				
		Prior recurrence rate					
		Primary	353 (59.6)				
		≤1 rec/year	108 (18.2)				
		>1 rec/year	85 (14.4)				
		unknown	46 (7.8)				

Study	N patients	Patient Characteristics	Follow-up	Outcomes	Prognostic factors	Comments
		Histopathology Pure UC 572 (96.6) UC with other elements 20 (3.4) Intravesical therapy None 311 (52.5) Chemo 189 (31.9) BCG 92 (15.5) EORTC recurrence risk (n=372) Low 12 (3.2) Intermediate 344 (92.5) Int-Low 186 (50) Int-High 158 (42.5) High 16 (4.3)				
Hernandez 2011 Spain 1998-2008	N=417 Mean age 68.8 years 84% M / 16% F	Stage n(%) Ta 227 (58.1) T1 164 (41.9) Tumour size <3cm 223 (59.8) ≥3cm 150 (40.2) Concomitant CIS Yes 14 (3.4) No 403 (96.6) No. of tumours 1 283 (70.8) 2-7 115 (28.8) >7 2 (0.5) Grade (WHO 1973) G1 220 (54.7) G2 142 (35.3) G3 40 (10) Prior recurrence rate Primary 219 (52.5) <1 rec/year 167 (40) >1 rec/year 31 (7.4) Intravesical therapy MMC single 274 (70.3)	Median 59 months	Recurrence Progression (to muscle-invasive status)	Same as Sylvester (2006) EORTC study	Validation of EORTC tables

Study	N patients	Patient Characteristics	Follow-up	Outcomes	Prognostic factors	Comments
		dose | BCG | 30 (8.2) MMC course | 14 (3.3) EORTC recurrence score 0 | 86 (20.6) 1-4 | 207 (49.6) 5-9 | 118 (28.3) 10-17 | 6 (1.4) EORTC progression score 0 | 69 (16.8) 2-6 | 200 (48.8) 7-13 | 126 (30.7) 14-23 | 15 (3.7)				
Altieri 2012 Italy 2002-2011	N=259 Median age 71 (43-90) 78% M / 22% F 73% of all patients had single MMC 40mg. 57% intermediate risk induction and 12-month maintenance chemo and 23% BCG. 87.5% high risk induction and 12-mo maintenance BCG. 22% re-TURB. All high risk patients received re-TUR.	Stage n(%) Ta | 161(62.2) T1 | 98 (37.8) Tumour size <3cm | 227 (87.6) ≥3cm | 32 (12.4) Concomitant CIS Yes | 7 (2.7) No. of tumours 1 | 131 (50.6) 2-7 | 115 (44.4) ≥8 | 13 (5) Grade (WHO 1973) G1 | 94 (36.3) G2 | 114 (44) G3 | 51 (19.7) Recurrence Primary | 185 (71.4) Recurrent | 74 (28.6) Intravesical therapy MMC single dose | 189 (73) EORTC recurrence score 0 | 38 (14.7)	Median 72 months, range 12-99	Recurrence Progression	NA – validation of EORTC rates of progression and recurrence	

Study	N patients	Patient Characteristics	Follow-up	Outcomes	Prognostic factors	Comments
		1-4: 112 (43.2) 5-9: 92 (35.5) 10-17: 17 (6.6) EORTC progression score 0: 52 (20) 2-6: 120 (46.3) 7-13: 64 (24.7) 14-23: 23 (8.9)				
Park 2009 1989-2005 South Korea	N=144 84% M/ 16% F Median age 63 yrs All T1G3 undergoing surveillance, 119 (82.6%) treated with IVT after TUR: 115 BCG, 2 MMC, 2 epirubicin. IVT 2 wks after TUR and maintenance BCG not given except in 3 patients	Tumour size <3cm: 92 (63.9) ≥3cm: 52 (36.1) Concomitant CIS Yes: 17 (11.8) No: 127 (88.2) Multiplicity Single: 56 (38.9) Multiple: 88 (61.1) Lymphovascular invasion Yes: 9 (6.3) No: 135 (93.8) Intravesical therapy No: 25 (17.4) Yes: 119 (82.6) Gross morphology Papillary: 85 (59) Non-papillary: 59 (41) Microscopic morphology Papillary: 93 (64.6) Non-papillary: 51 (35.4) Proper muscle Present: 106 (73.6) Absent: 38 (26.4)	Median 52.5 mo	Recurrence Progression		
Alkibay 2009 2002-2006 Turkey	N=6 with micro papillary pattern (MPP), n= 125 without MPP. Treated according to	Patient characteristics not reported separately for NMIBC and MIBC	Median=27.2 mo (12-72)	Progression	Micropapillary pattern (absent or present) -the extent of micropapillary morphology was determined as a tumour percentage	

Study	N patients	Patient Characteristics	Follow-up	Outcomes	Prognostic factors	Comments
	EAU guidelines Mean age 64 years (24-93)					
Tilki 2012 1984-2003 USA	N=101 clinical or pathologic stage T1 without nodal mets treated with RC with bilateral lymphadenectomy	N (%) Male 86 (85) Female 15 (15) Clinical stage (pre RC) Ta 5 (5) Tis 5 (5) T1 91 (90) Post RC pathological stage T0 17 (17) Ta 6 (6) Tis 21 (21) T1 57 (56) Grade (higher of pre-RC and post-RC) 2 10 (10) 3 91 (90) Concomitant CIS on RC 63 (62) Prostate involvement 10 (12) LVI (n=97) Yes 6 (6) No 91 (94)	Median 38 (IQR 22-77) months for patients alive at last visit.	Recurrence-free survival. 4/6 patients with LVI experiences disease recurrence. Disease recurred in 12 patients (all who had LVI or CIS on RC) Cancer-specific survival: 3/6 patients who had LVI died from bladder cancer. All 7 cancer-specific deaths occurred in patients who had concomitant CIS or LVI.	LVI defined as presence of tumour cells within endothelium lined space without underlying muscular walls.	Retrospective study. Low number of patients with LVI. Low number of events
Branchereau 2013 1994-2009 France	N=108 high grade bladder cancer pT1.	Mean age 69.1 ±13.1y Male 81 (87%) History of NMIBC 20 (19%) History of CIS 17 (16%) Unifocal 56% Multifocal 44% Diameter <3cm 72% pT1a 64% pT1b 36%	Mean follow-up 47.8 ±41.2 months	Overall survival	LVI defined as presence of tumour cells within a space limited the endothelium surrounded by a layer of smooth muscle cells. Assessed on the first TURBT.	Retrospective study. Hazard ratios not reported.

Study	N patients	Patient Characteristics		Follow-up	Outcomes	Prognostic factors	Comments
		LVI	39 (36%)				
		Cystectomy	19 (18%)				
Xylinas 2013 2000-2007 Multicentre	N=4689 patients who underwent TURBT for NMIBC. Pure Tis excluded. Re-resection at surgeons discretion within 2-6 weeks. 51% had immediate single postoperative chemotherapy (MMC). All BCG patients were proposed some form of maintenance (at least 1 yr). None had UTUC.		N (%)	Median 46 months for those without recurrence and 57 months for those without progression.	Recurrence – first relapse in bladder regardless of stage Progression – tumour relapse at stage T2 or higher in bladder or prostatic urethra.	EORTC scoring system and CUETO risk tables.	Retrospective study.
		Median age	67 (59-74)				
		male	3721 (79)				
		female	968 (21)				
		Primary	3284 (70)				
		Recurrent	1405 (30)				
		≤1 recurrence/ year	727 (16)				
		1 tumour	2865 (61)				
		2-7 tumours	1816 (39)				
		≥8 tumours	8 (<1)				
		<3cm diameter	3698 (79)				
		≥3cm	991 (21)				
		Ta	3030 (65)				
		T1	1659 (35)				
		G1	1419 (30)				
		G2	1428 (30)				
		G3	1842 (39)				
		Concomitant CIS	223 (5)				
		Adjuvant BCG	538 (11)				
Xu 2013 2003-2010 China	N=363 patients who underwent TUR for primary and recurrent NMIBC. Primary CIS, nonurothelial cancer, peri-operative radiotherapy, and systemic chemotherapy or cystectomy after TURBT excluded. Re-TUR in high risk patients. No BCG. Immediate adjuvant intravesical chemotherapy in all but		N (%)	Median 36 months (range 4-115)	Recurrence (rate 45.5%) within median 14 months. Progression to MIBC (5.8%)	EORTC scoring system and CUETO risk tables. Recurrence : Low risk 19%; low-intermediate risk 44%; intermediate-high risk 34%; high risk 3% Progression: Low risk 24%; low-intermediate risk 52%; intermediate-high risk 19%; high risk 5%	Retrospective study. Few progression events.
		Mean age	66.1				
		male	265(73)				
		female	98 (27)				
		Primary	212 (58)				
		Recurrent	151 (42)				
		≤1 recurrence/ year	36 (9.9)				
		1 tumour	184 (51)				
		2-7 tumours	172 (47)				
		≥8 tumours	7 (2)				
		<3cm diameter	339 (93)				
		≥3cm	24 (7)				
		Ta	273 (75)				
		T1	90 (25)				
		G1	153 (42)				

Study	N patients	Patient Characteristics	Follow-up	Outcomes	Prognostic factors	Comments
	77 patients. Additional chemo 7-15 days after resection (epirubicin or pirarubicin) for8 weeks with additional monthly maintenance	G2: 159 (44) G3: 51 (14) Concomitant CIS: 11 (3)				
Olsson 2013 1992-2001 Sweden Retrospective	211 with primary stage T1 UCB. No routine random biopsy, early re-resection in 31 patients. 51 had BCG or chemotherapy. 6 RC and 6 RT	Median age 74y 17% female 80% had recurrence, 39% progression. 32% died from bladder cancer. 25 had concomitant CIS LVI invasion (n=16, 7.5%)	Median 60 months (range 3 to 192 months)	Recurrence Progression Death from bladder cancer.	LVI assessed on the routinely stained histological slides: LVI present/LVI suspected and LVI not present. LVI defined as tumour cells within or attached to the wall of a vascular space.	Retrospective study. Few patients with LVI (n=16).
Lammers 2014 Netherlands 1987-2010 Patient data retrospectively reviewed from prospective studies	728 patients from 3 Dutch studies including patients treated with complete TURBT and adjuvant intravesical epirubicin (n=518) or MMC (n=210).	N (%) Male: 600 (83) Female: 127 (18) Median age: 68.3 (33-86) Primary: 381 (52) Recurrent: 347 (48) History of CIS: 7 (1) Previous treatment: 619 (86) Ta: 568 (78) T1: 160 (22) G1: 294 (40) G2: 346 (48) G3: 88 (12) Single: 184 (25) <3cm: 574 (79) EUA low risk recurrence: 1 (0.1) EUA intermediate recurrence: 668 (92) EUA high recurrence: 59 (8) EUA low risk progression: 19 (3)	Median follow-up 28.2 months (2-76)	Recurrence Progression	EORTC scoring system used to reclassify patients. Observed recurrence and progression compared against those predicted from EORTC	317 patients with missing data

Study	N patients	Patient Characteristics		Follow-up	Outcomes	Prognostic factors	Comments
		EAU intermediate progression	524 (72)				
		EAU high progression	185 (25)				

3.2 Managing non-muscle-invasive bladder cancer

3.2.1 Intravesical therapy

Review question: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk, intermediate and high-risk non-muscle invasive bladder cancer?

Rationale

The risk of recurrence can be reduced by the administration of chemotherapy medication, in liquid form, into the bladder (intravesical chemotherapy). This can be done immediately, or shortly after telescopic removal of the tumour (transurethral resection), and subsequently, as a planned outpatient procedure. Several different chemotherapy drugs have been used, and studied.

There is debate (and variation) about which patients with which sort of LRNMIBC should be treated with intravesical chemotherapy, including whether patients with small or very small tumours should be treated, and what sort of recurrent tumours should be treated.

The advantage of not being treated is that no side effects of treatment are suffered, whereas the benefit of being treated may be that recurrence becomes less likely. The disadvantage of not being treated is that there is no reduction in the risk of recurrence, and the disadvantage of being treated is that side effects (such as urine infection, bladder pain, and genital rashes) are suffered.

Instillation of BCG vaccine is also offered to some patients who have recurrence of LRNMIBC following previous intravesical chemotherapy. The side effects of BCG include irritation of the bladder, urine infection, occasional rare consequences probably related to the effects of BCG on the body's immune system, and very rare infections with the BCG bacteria. These side effects need to be considered in a consideration of the advantages and disadvantages of BCG equivalent to the consideration of the advantages and disadvantages of intravesical chemotherapy.

The topic is being considered because LRNMIBC is common, recurrence is common, and because intravesical chemotherapy has significant efficacy, but the pattern of disease is not homogeneous, meaning the grade, size, number and recurrence history of tumours can combine to present a significantly mixed group of patients and tumours, so that determining which patients with which tumours should be treated is an important area for guidance.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with newly diagnosed NMIBC following first TUR Subgroups: Male/female Low/intermediate-risk NMIBC	Intravesical chemotherapy/BCG Single installation/ Induction course/ Maintenance BCG Mitomycin C Epirubicin	Each other None	• Overall survival • Disease-specific survival • Disease progression • Recurrence • Treatment-related morbidity • Treatment-related

High-risk NMIBC	Doxorubicin (adriamycin) Gemcitabine Eoquin		mortality • Health-related quality of life inc patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (EH) using a systematic review and randomised trials filter, with no date limit.

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. Systematic reviews and randomised trials were selected for this review.

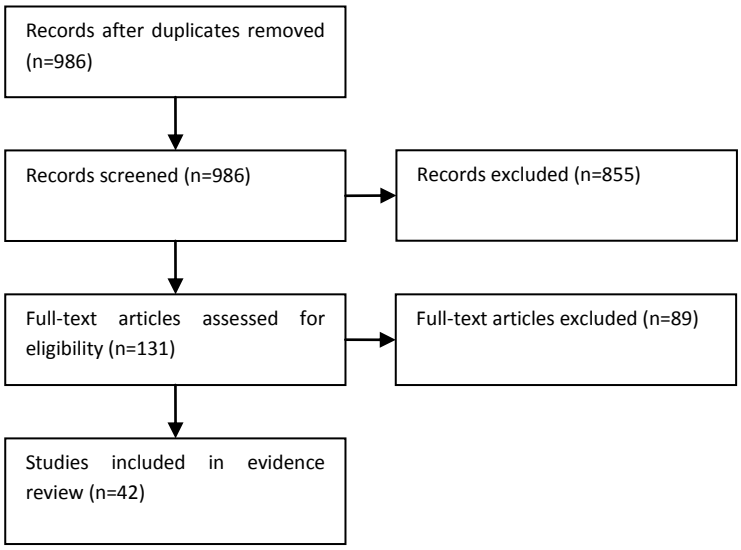
Data synthesis

Dichotomous data (e.g. number of events and number of participants) from systematic reviews and randomised trials were presented in RevMan when possible. Overall risk ratios are presented in GRADE and forest plots are also provided. The evidence was analysed by gender and risk subgroups where appropriate. Consideration was given to immediate single installation therapy, induction therapy and maintenance therapy. Intravesical chemotherapy agents were analysed together with specific agents included as subgroups.

RESULTS

Result of the literature searches

Figure 36. Study flow diagram



Study quality and results

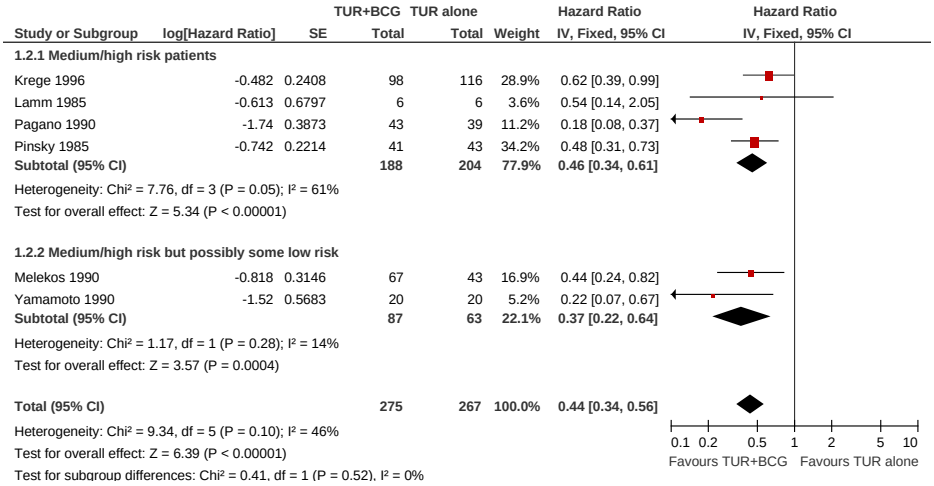
The quality and results of the included studies are summarised in GRADE evidence profiles (Tables 39-65).

Narrative summary of evidence

TUR + BCG versus TUR alone

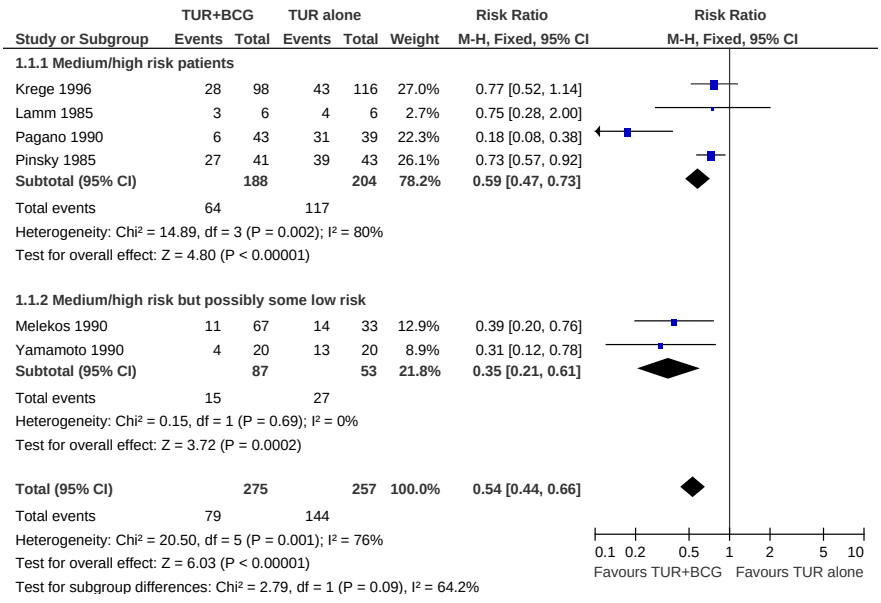
Moderate quality evidence from a meta-analysis (Shelley *et al.,* 2000) of 585 medium-high risk patients from six randomised trials (all published prior to 1999) produced an overall HR of 0.44 (95% CI 0.34 to 0.56), indicating a 56% reduction in the possibility of tumour recurrence for TUR+BCG compared to TUR alone.

Figure 37. TUR+BCG versus TUR alone. Outcome: recurrence-free survival (Shelley 2000)



29% (79/275) of the BCG group presented with a recurrence at 12 months, compared to 56% (144/257) in the TUR only group with a risk ratio (RR) of 0.54 (95% CI 0.44 to 0.66), indicating a 46% reduced risk of recurrence at 12 months with BCG compared to TUR alone.

Figure 38. TUR+BCG versus TUR alone. Outcome: Recurrence at 12 months (Shelley 2000)



Another meta-analysis (Han, 2006) provided high quality evidence from 9 RCTs and controlled observational cohort studies (1100 patients) published between 1997 and 2005. BCG+TUR was associated with a lower risk of recurrence compared to TUR alone (RR 0.59, 95% CI 0.45 to 0.78).

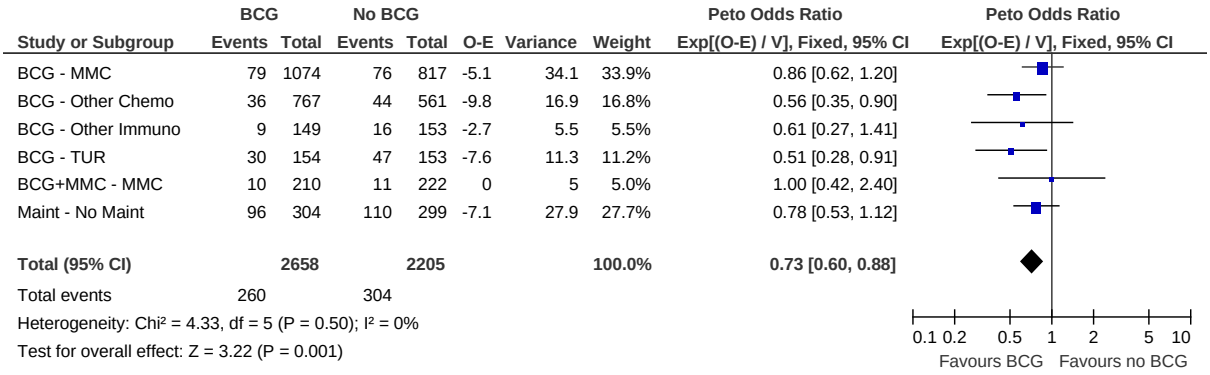
The systematic review by Shelley (2000) reported that the main toxicities associated with BCG were urinary frequency (71%), cystitis (67%), haematuria (23%), and fever (25%). No BCG sepsis or deaths were reported.

TUR + BCG versus TUR alone or TUR + another treatment

Moderate quality evidence from a meta-analysis (Pan, 2014) of 48 RCTs and observational cohort studies (9482 patients) reported a pooled random effects OR for recurrence of 0.59 (95% CI 0.49 to 0.71) for TUR + BCG compared to those treated with resection alone or TUR plus another treatment other than BCG, with significant heterogeneity across studies ($p<0.01$). Evidence from an earlier meta-analysis (Han, 2006) suggested that the effect of BCG is less conclusive when induction BCG only is given compared to control groups (RR 0.99, 95% CI 0.77 to 1.28). In the maintenance BCG subgroup the combined random effect RR is 0.65 (95% CI 0.48 to 0.88), suggesting that maintenance BCG reduces the risk of recurrence by 35%. There were no differences when studies were stratified by BCG strain. Another meta-analyses (Pan, 2008) of 13 trials or controlled studies, which compared maintenance BCG versus no maintenance BCG for T1G3 bladder cancer, reported that overall 41% of the maintenance BCG group recurred compared to 45% in the control group (RR 0.73, 95% CI 0.61, 0.88).

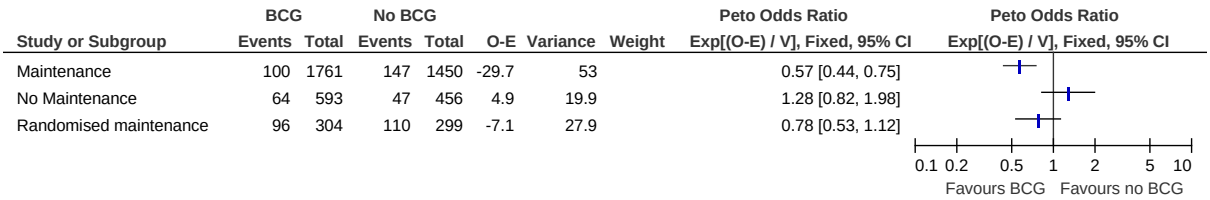
High quality evidence from one meta-analysis (Sylvester 2002) of 24 randomised trials with 4863 patients reported that the risk of progression was 27% lower for patients treated with BCG compared to those treated with either resection alone or TUR plus another treatment other than BCG (HR 0.73, 95% CI 0.60 to 0.88). There was no difference in the size of treatment effects across the different control groups (see figure 39 below) or according to the strain of BCG used.

Figure 39. TUR+BCG versus TUR+other treatments. Outcome: Progression (Sylvester, 2002)



No reduction in the risk of progression was seen in the four trials where maintenance BCG was not used (HR 1.28, 95% CI 0.82 to 1.98). In trials where maintenance BCG was used, the risk of progression was lower for those treated with BCG compared to the control groups (HR 0.57, 95% CI 0.44 to 0.75).

Figure 40. TUR+BCG versus TUR+another treatment. Outcome: Progression (Sylvester, 2002)



There were no significant differences in overall survival (HR 0.89, 95% CI 0.75 to 1.06) or disease-specific survival (HR 0.81, 95% CI 0.57 to 1.13) between those treated with BCG and those in the control groups. The two meta-analyses by Han (2006) and Pan (2008) both reported that drug-related and systemic toxicities were significantly more frequent in the BCG groups than chemotherapy or immunotherapy groups.

TUR + chemotherapy versus TUR alone

One systematic review and meta-analysis of 11 studies and 3703 patients with primary bladder cancer reported a Peto Odds Ratio (pOR) of 0.56 (95% CI 0.48 to 0.65) for 1-year recurrence in favour of adjuvant intravesical chemotherapy compared to TUR alone (Huncharek, 2000). However, significant statistical heterogeneity was reported and sensitivity analyses were conducted. The data were stratified by duration of treatment, which indicated that short-term therapy (≤2 months duration) reduced recurrence at 1-year (pOR 0.70, 95% CI 0.55 to 0.90) and 2-years (pOR 0.68, 95% CI 0.54 to 0.85) by approximately 30%, as compared to TUR alone (moderate quality evidence). The pooled pOR for 5 trials where patients received 2 years of chemotherapy was 0.27 (95% CI 0.19 to 0.39), indicating a 73% reduction in the risk of recurrence at 2 years for those treated with chemotherapy.

One systematic review and meta-analysis of 8 studies and 1609 patients with recurrent bladder cancer reported a pooled pOR for 1-year recurrence of 0.62 (95% CI 0.51 to 0.76), in favour of chemotherapy over TUR alone, with no evidence of statistical heterogeneity (moderate quality evidence). For the 2- and 3-year recurrence rates, significant statistical heterogeneity was reported, which was not accounted for by treatment duration. Therefore, moderate quality evidence was reported from the data when stratified by drug type (adriamycin versus other drugs). The pOR for 2-year recurrence of studies using adriamycin was 0.57 (95% CI 0.43 to 0.75), with no significant heterogeneity, indicating that drug type was a major contributor to outcome heterogeneity. Drugs other than adriamycin showed a reduction in 2-year recurrence of 73% (versus 43% for adriamycin) with an pOR of 0.27 (95% CI 0.19 to 0.37). The non-overlapping CIs indicate a significant difference in tumour reduction effect, with adriamycin appearing less effective than other drugs (e.g. thiotepa, MMC).

A systematic review and meta-analysis (Pawinski, 1996) provided moderate quality evidence from 6 randomised trials, which suggests there is uncertainty about the effect of intravesical chemotherapy on progression (HR 1.19, 95% CI 0.97 to 1.47), overall survival (HR 1.1, 95% CI 0.95 to 1.27), and disease-specific survival (HR 1.1, 95% CI not reported but effect size was non-significant), compared to TUR alone.

TUR + one post-operative instillation of chemotherapy versus TUR alone

Low to moderate quality evidence was provided from a systematic review and meta-analysis of 18 trials comparing one post-operative dose of chemotherapy with TUR alone (Abern, 2013). 36.6% (577/1576) of those in the TUR + chemotherapy group experienced a recurrence compared with 50.4% (769/1527) of those treated with TUR alone (RR 0.67, 95% CI 0.56 to 0.79), with significant statistical heterogeneity. This corresponds to a number needed to treat of 7.2 patients to avoid one recurrence. Gemcitabine and interferon α-2b did not show a benefit on recurrence, whereas the other chemotherapy agents did. The pooled RR for mitomycin C and epirubicin was 0.71 (95% CI 0.64 to 0.78), in favour of chemotherapy, with no clear dose-response relationship. Individual tumour risk factors such as recurrence, multiplicity, stage, and grade, did not appear to alter the efficacy of a single dose of chemotherapy. Funnel plots suggested the existence of publication bias with small trials contributing disproportionately to the protective effect of chemotherapy. A meta-analysis (Sylvester, 2004) of 7 trials (1476 patients) reported mild, transient, irritative bladder symptoms including dysuria, frequency and macroscopic haematuria, in approximately 10% of patients treated with intravesical chemotherapy.

TUR + chemotherapy versus TUR + BCG

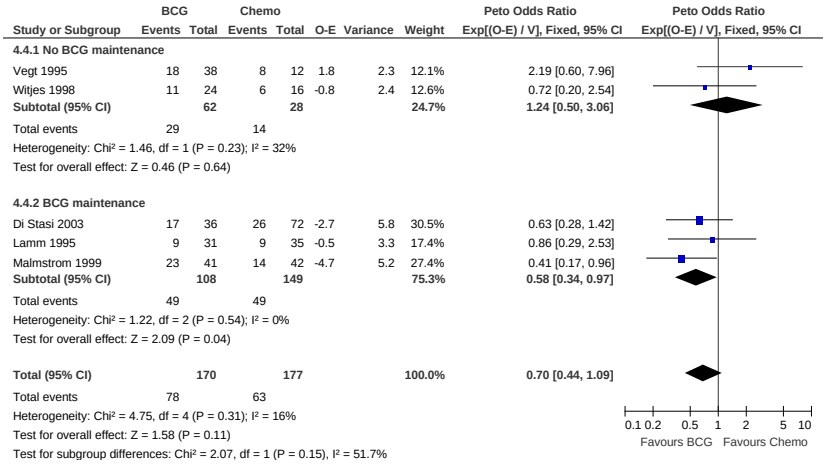
One systematic review of 9 trials and 2261 patients (Huncharek, 2003) reported low quality evidence of an overall OR for 1-year recurrence of 0.89 (95% CI 0.74 to 1.07), with significant heterogeneity. Heterogeneity persisted despite stratification by chemotherapy drug type. A sensitivity analysis was therefore performed stratifying by previous intravesical chemotherapy. Pooling all studies that enrolled patients with prior chemotherapy (1480 patients) provided moderate quality evidence, with an OR of 0.54 (95% CI 0.43 to 0.69), in favour of BCG. This reflects a 46% reduction in tumour recurrence at 1-year among patients treated with BCG versus chemotherapy, and a lack of statistical heterogeneity. Pooling data from 2 studies which excluded patients previously treated with chemotherapy gave an OR of 1.82 (95% CI 1.37 to 2.41), in favour of chemotherapy. This suggests that amongst patients not previously treated, intravesical chemotherapy (MMC) reduces tumour recurrence by 82% versus BCG. Similar results were found for 2-year and 3-year recurrence when stratified by previous therapy.

One systematic review of 8 randomised trial and 2427 patients (Huncharek, 2004) randomised to either adjuvant intravesical BCG or chemotherapy provided moderate quality evidence of an OR for progression of 1.24 (95% CI 0.95 to 1.61), in favour of BCG. The confidence intervals include the value of no effect which suggests uncertainty of a difference between the two treatments in terms of progression. The total number of events in each arm was not reported. Subgroup analyses of MMC vs. BCG (4 trials, 1478 patients) provided an OR of 1.04 (0.76 to 1.42) suggesting no difference in risk of progression. The pooled OR of the two trials (781 patients) which excluded patients who had previously been treated with intravesical chemotherapy was 0.75 (0.45 to 1.25) in favour of MMC. In trials which included patients previously treated with chemotherapy the OR was 1.49 (1.09 to 2.03) in favour of BCG.

One meta-analysis (Sylvester 2005) of 9 randomised trials and 700 patients with CIS provided moderate quality evidence that 34% of complete responders treated with BCG and 50% of complete responders treated with chemotherapy recurred during follow-up (HR 0.47, 95% CI 0.31 to 0.73) in favour of BCG. 47% of patients treated with BCG and 26% treated with chemotherapy had no evidence of disease during follow-up, an absolute difference of 20% and a relative reduction of 59%

in the odds of treatment failure on BCG (HR 0.41, 95% CI 0.30 to 0.56). BCG only appeared to be superior to MMC in the trials where maintenance BCG was given (see Figure 41). Data on progression was less conclusive with an HR of 0.74 (95% CI 0.45 to 1.22). Overall survival was reported in three studies (407 patients). 35.9% of patients treated with chemotherapy and 34.2% treated with BCG therapy died from any cause. Two trials reported disease-specific survival. 13.3% of patients treated with chemotherapy and 10.5% of patients treated with BCG died due to bladder cancer.

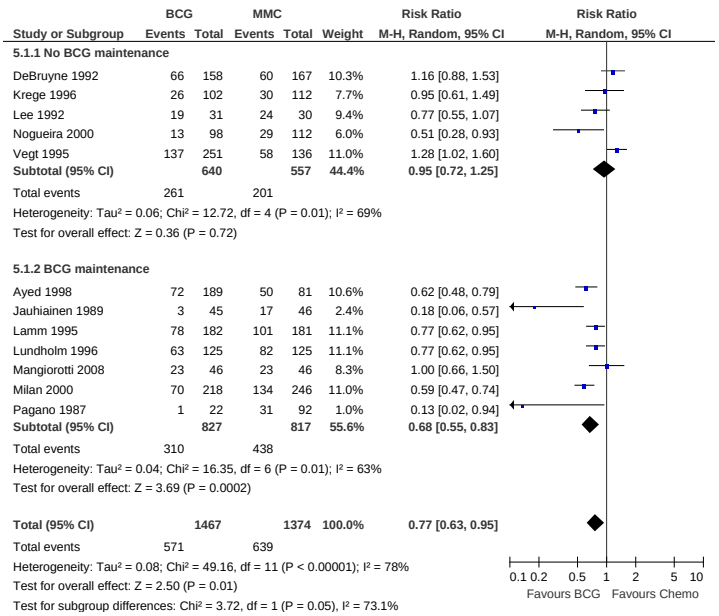
Figure 41. BCG versus MMC according to BCG maintenance. Outcome: no evidence of disease (Sylvester, 2005)



BCG vs. MMC

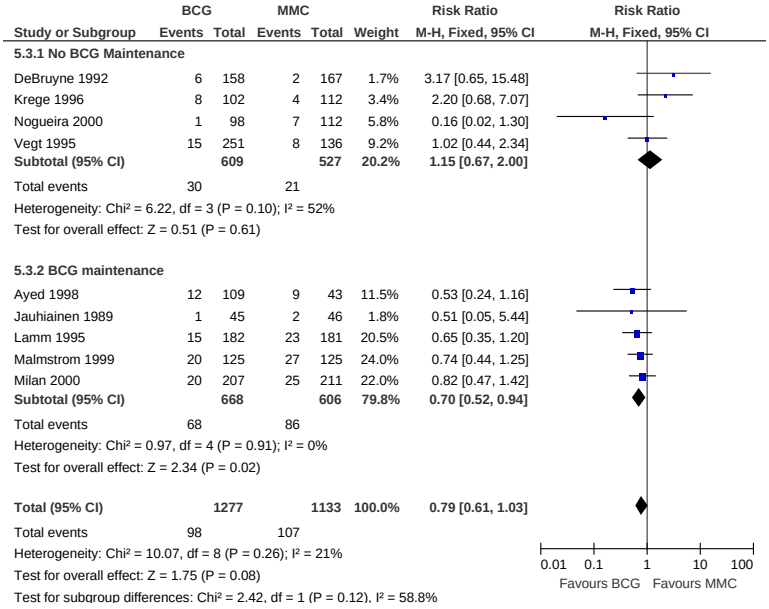
Moderate quality evidence was reported from one systematic review and meta-analysis (Bohle 2003) of 2749 patients from 9 prospective trials and 2 observational studies. A further trial of 92 patients was indentified and added to the pooled analysis for overall recurrence and recurrence by maintenance therapy (Mangiarotti 2008). The overall RR for recurrence was 0.77 (95% CI 0.63 to 0.95) in favour of BCG over MMC. BCG maintenance showed superiority over MMC with an RR or 0.68 (95% CI 0.55 to 0.83) (Figure 42). A dose response relationship was observed, where at least 12 instillations of BCG are required for its relevant superiority over MMC. The studies using BCG strain RIVM or RIVM plus TICE reported much weaker efficacy results for BCG than any other study in the meta-analysis. Cystitis was more frequent in the BCG group compared to the MMC group (53.8% vs. 39.2%, p<0.001). Local and systemic toxicities were more frequent in the BCG group, except for allergy and skin reactions which were more common in MMC group. The risk of cystitis was no different between maintenance BCG and no maintenance BCG. No deaths from sepsis were reported in either arm.

Figure 42. BCG versus MMC by maintenance. Outcome: Recurrence (Bohle, 2003)



Moderate quality evidence from one meta-analysis including 1277 patients (Bohle, 2004) reported no difference between BCG and MMC in terms of disease progression. Overall, 7.7% (98/1127) of the BCG group progressed versus 9.4% (107/1133) of the MMC group (RR 0.79, 95% CI 0.61 to 1.03). However, BCG did show superiority over MMC in the subgroup of BCG maintenance trials (RR 0.70, 95% CI 0.52 to 0.94). There were no significant confounding effects when stratified by BCG strain, BCG dose, risk group, MMC dose, number of MMC instillations, follow-up duration, or year of publication.

Figure 43. BCG versus MMC by BCG maintenance. Outcome: Progression (Bohle, 2004)

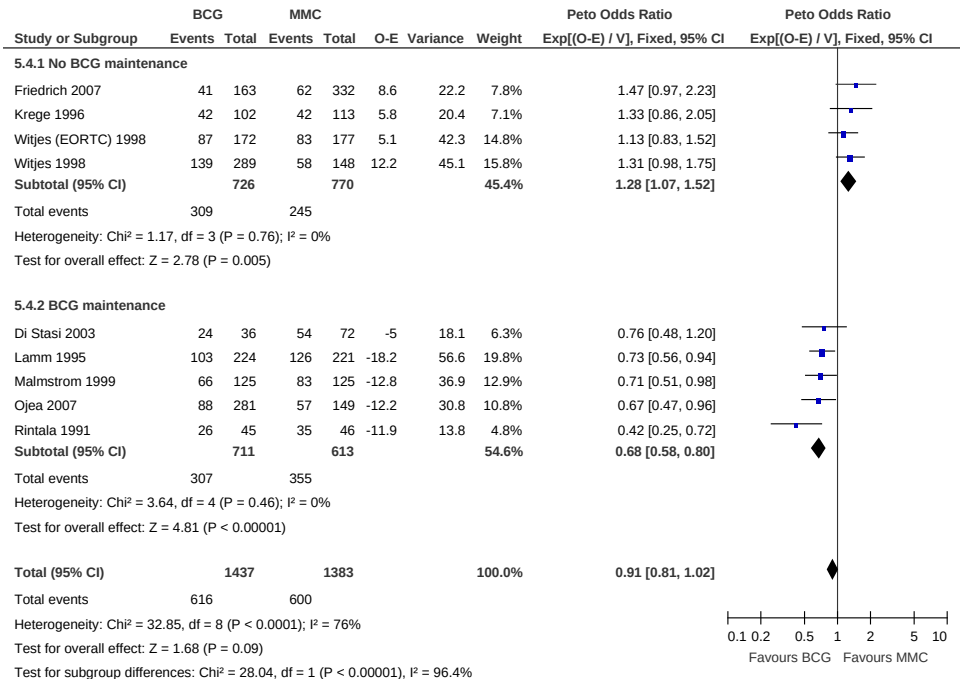


High quality evidence from a meta-analysis of individual patient data (Malmstrom, 2009) including 9 trials (2820 patients) reported that in trials with BCG maintenance, there was a 32% reduction in the risk of recurrence with BCG compared to MMC (HR 0.68, 95% CI 0.58 to 0.8), whilst there was a 28%

risk increase for BCG trials without maintenance (HR 1.28, 95% CI 1.07 to 1.52) (see Figure 44). Maintenance BCG was more effective than MMC in both patients previously treated and those not previously treated with intravesical chemotherapy.

Moderate quality evidence from 7 trials (1880 patients) in the IPD meta-analyses reported that after a median follow-up of 4.8 years, 12% of patients progressed to MIBC and 24% died (of those 30% died from bladder cancer). There were no significant differences between MMC and BCG for these end-points, even when stratified by BCG maintenance and patient risk groups.

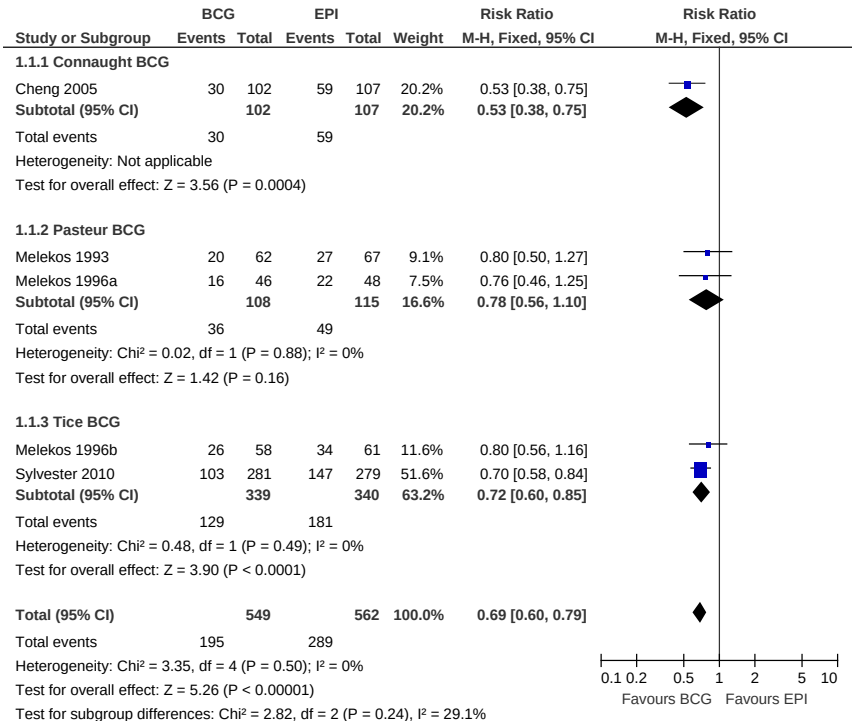
Figure 44. BCG versus MMC, by BCG maintenance. Outcome: Time to first recurrence (Malmstrom, 2009)



BCG versus Epirubicin (EPI)

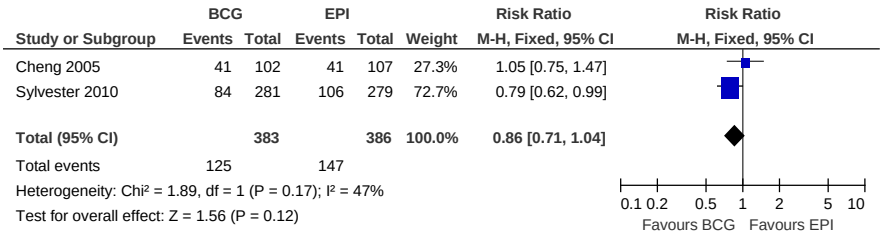
One systematic review of 5 randomised trials (Shang, 2011), reported that the risk of recurrence was reduced in patients treated with BCG (35.5%) compared to EPI (51.4%) with a RR of 0.69 (95% CI 0.60 to 0.79), in favour of BCG. Subgroup analyses demonstrated that two trials which treated patients with Pasteur strain BCG found no significant difference in recurrence between BCG and EPI (RR 0.78, 95% CI 0.56 to 1.10).

Figure 45. BCG versus EPI. Outcome: Recurrence (Shang, 2011)



There was no significant difference between BCG and EPI for disease progression (RR 0.78, 95% CI 0.54 to 1.13). No differences were found for overall mortality (2 studies) or disease-specific mortality (2 studies). However, overall mortality was less frequent in the TICE BCG group compared to the EPI group in the study by Sylvester (2010) (RR 0.79, 95% CI 0.62 to 0.99) (see Figure 46). Drug-induced cystitis (54% versus 32%), haematuria (31% versus 16%), and systemic side-effects (35% versus 1%) were significantly more frequent with BCG than EPI. However, there was significant heterogeneity between trials for systemic side-effects due to the frequency of BCG administration. There were no significant differences for delayed or terminated treatment due to adverse events between BCG and EPI (9% versus 7%) (RR 0.91, 95% CI 0.41 to 2.04).

Figure 46. BCG versus EPI. Outcome: Overall survival (Shang, 2011)



BCG versus Gemcitabine

One systematic review by Jones (2012) reported 3 studies comparing Gemcitabine with BCG (one of these trials and the trial comparing BCG with MMC included patients who had failed BCG therapy which is covered in another topic). Heterogeneity between trials prevented pooling of data. One trial of 80 patients at intermediate risk of recurrence (primary Ta-T1, no CIS) provided low quality evidence that BCG (no maintenance) and Gemcitabine showed similar rates of recurrence (25% vs. 30%) and progression, with significantly more adverse effects with BCG (Bendary 2011). Moderate

quality evidence was provided by one trial of 64 high risk patients, which reported that recurrence rate was higher for Gemcitabine than BCG (53% vs. 28%) and time to recurrence was shorter with Gemcitabine (25.6 months vs. 39.4 months). No patients in either group had disease progression at a mean follow-up of 44 months. Local and systemic toxicity were similar between groups. In this trial maintenance therapy for non-recurring patients in each group was up to 36 months duration (Porena, 2010).

Duration of BCG

In 6 meta-analyses (Sylvester, 2002; Han, 2006; Sylvester, 2005; Malmstrom, 2009; Bohle, 2003; Bohle 2004) BCG was superior to chemotherapy only if a maintenance schedule was used.

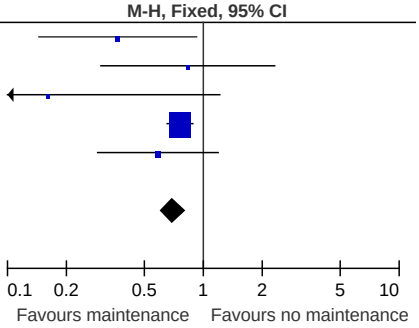
Six trials of maintenance versus induction BCG were indentified which varied in the population included and the schedule and duration of maintenance therapy. High quality evidence from five of these trials demonstrated that 53.9% of patients in the BCG induction arm had a recurrence, compared to 37.6% in the maintenance BCG arm (RR 0.70, 95% CI 0.60 to 0.81). Moderate quality evidence from 5 trials showed that there were no overall differences in progression (27.6% versus 31.8%). However, this data should be interpreted with caution due to the variation in BCG maintenance schedules and the duration of follow-up across studies.

Figure 47. Maintenance versus induction BCG. Outcome: Recurrence

	Maintenance BCG		Induction BCG			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Hinotsu 2010	5	41	14	42	7.5%	0.37 [0.14, 0.92]
Hudson 1987	5	21	6	21	3.2%	0.83 [0.30, 2.31]
Koga 2010	1	24	7	27	3.6%	0.16 [0.02, 1.21]
Lamm 2000	108	192	142	192	76.8%	0.76 [0.65, 0.88]
Palou 2007	10	65	16	61	8.9%	0.59 [0.29, 1.19]
Total (95% CI)		**343**		**343**	**100.0%**	**0.70 [0.60, 0.81]**
Total events	129		185			

Heterogeneity: Chi² = 5.54, df = 4 (P = 0.24); I² = 28%

Test for overall effect: Z = 4.68 (P < 0.00001)



Two controlled trials published in 1987 (Hudson 1987; Badalament 1987) showed no significant benefit of maintenance BCG therapy on recurrence. A study of 384 patients with recurrent bladder cancer or CIS were randomised to BCG induction alone or BCG induction plus 3-week maintenance schedule for up to 3-years (Lamm, 2000). With a median follow-up of 7 years, maintenance BCG significantly improved median recurrence-free survival (from 36 months to 77 months, p<0.0001). 5-year survival also increased from 78% to 83% with BCG maintenance, but this difference was non-significant (p=0.08). A Japanese Cooperative study (Hinotsu, 2010) of 115 patients with multiple or recurrent NMIBC without CIS, reported that 2-year recurrence-free survival was significantly longer in the combined BCG groups compared with 9 weeks Epirubicin therapy, and for BCG maintenance versus induction BCG only (Recurrence rate: 12% versus 33%). No difference in progression was reported between BCG maintenance and non-maintenance, although there were no cases of progression in the maintenance arm. A further study randomised 53 patients (88% with CIS) who

had achieved a complete response after induction BCG therapy into maintenance (4 instillations) therapy or observation (Koga, 2010). The 2-year recurrence free survival was higher in the maintenance group (95.8%) than the observation group (74.1%), although this was not significant. Two patients in each group died during follow-up. There were no significant changes in quality of life scores (EORTC-QLQ) in either group from induction treatment to 14 months after randomisation. Very low quality evidence from one observational study reported that overall quality of life was moderate, and more patients rated it as good during maintenance than during induction therapy (Mack 1996). Drug-related toxicities, such as dysuria, haematuria and fever, were generally more prevalent with maintenance BCG than with induction BCG.

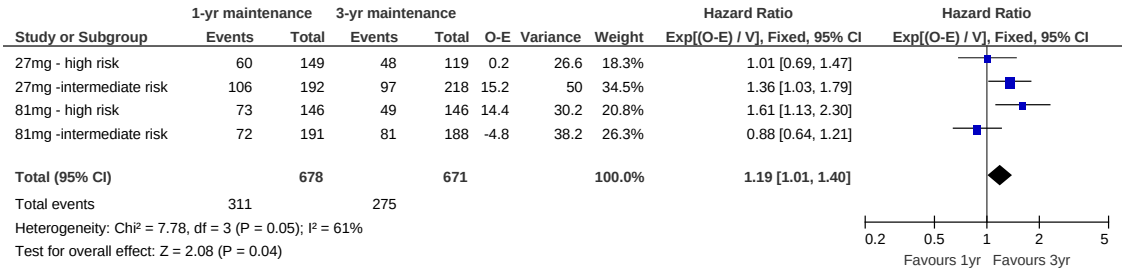
Dose of BCG

Two trials provided moderate quality evidence of no difference in recurrence, progression, overall survival and disease-specific survival between one-third (27mg) dose and full dose (81mg) BCG. One trial (Martinez-Pineiro, 2002) included 500 patients (Ta/T1/CIS, G1-G3) and the other trial (Martinez-Pineiro, 2005) included 155 patients with T1G3 disease or CIS. Martinez-Pineiro (2002) reported that in patients with multifocal disease the standard dose was more effective against recurrences and progression than the reduced dose. Local toxicity was significantly reduced in the low dose BCG arm (53% versus 67%), and fewer patients had delayed instillations or withdrew from treatment. There were no differences between groups for severe systemic toxicities (3.8% versus 2.7%).

Moderate quality evidence from another CUETO group trial (Ojea, 2007) reported that there were no differences in recurrence-free survival between low dose BCG (27mg) and very-low dose BCG (13.5mg) in intermediate risk patients. There were no differences in time to progression and cancer-specific survival between the two BCG treatment groups. Rates of local (65.5% vs. 64.1%) and systemic (11.3% vs. 10.8%) adverse events were also similar between the two groups.

Moderate quality evidence was reported in one trial of 1355 patients randomised into 4 trial arms (Oddens, 2012). With a median follow-up of 7.1 years, there were no differences in recurrence, progression, overall survival and toxicity between one-third (27mg) dose and full dose (81mg) BCG. When results were stratified by maintenance and dose, one-third dose BCG with 1-year maintenance was suboptimal compared to full-dose BCG with 3-year maintenance (HR for disease-free interval 0.75, 95% CI 0.59 to 0.94). In intermediate-risk patients, 3 years of maintenance was more effective than 1 year in patients receiving one-third dose (HR 1.35, 95% CI 1.03 to 1.79) but not in patients receiving full-dose (HR 0.88, 95% CI 0.64 to 1.21). In high-risk patients, 3 years of maintenance was more effective than 1 year in patients receiving full dose (HR 1.61, 95% CI 1.13 to 2.30) but not in patients receiving one-third dose BCG (HR 1.01, 95% CI 0.69 to 1.47). There were no significant differences between treatment groups for the time to progression or overall survival.

Figure 48. 1-year of maintenance versus 3-year of maintenance BCG according to dose and risk group. Outcome: Disease-free interval (Oddens, 2012)



Evidence statements

TUR + BCG versus TUR alone

Moderate quality evidence from a meta-analysis (Shelley *et al.*, 2000) of 585 medium to high risk patients from six randomised trials produced an overall hazard ratio (HR) for recurrence-free survival of 0.44 (95% CI 0.34 to 0.56), indicating a 56% reduction in the risk of tumour recurrence for TUR+BCG compared to TUR alone. The main toxicities associated with BCG are urinary frequency (71%), cystitis (67%), haematuria (23%), and fever (25%). No BCG sepsis or deaths are reported.

TUR + BCG versus TUR + other treatment (chemotherapy or immunotherapy) or TUR alone

Moderate quality evidence from a meta-analysis (Pan *et al.*, 2014) of 48 RCTs and observational cohort studies (9,482 patients) reported a pooled random effects OR for recurrence of 0.59 (95% CI 0.49 to 0.71) for TUR + BCG compared to those treated with resection alone or TUR plus another treatment other than BCG, with significant heterogeneity across studies ($p<0.01$). Evidence from an earlier meta-analysis (Han & Pan, 2006) suggested that the effect of BCG is less conclusive when induction BCG only is given compared to control groups (RR 0.99, 95% CI 0.77 to 1.28). In the maintenance BCG subgroup the combined random effect RR is 0.65 (95% CI 0.48 to 0.88), suggesting that maintenance BCG reduces the risk of recurrence by 35%. Moderate quality evidence from a meta-analysis of 13 trials or controlled studies comparing maintenance BCG versus no maintenance BCG for T1G3 bladder cancer, reports that overall 41% of the maintenance BCG group recurred compared to 45% in the control group (RR 0.73, 95% CI 0.61, 0.88) (Pan *et al.*, 2008).

High quality evidence from one meta-analysis of 24 randomised trials with 4863 patients, suggests that the risk of progression was 27% lower for patients treated with BCG compared to those treated with either resection alone or TUR plus another treatment other than BCG (HR 0.73, 95% CI 0.60 to 0.88) (Sylvester *et al.*, 2002). No reduction in the risk of progression was seen in the four trials where maintenance BCG was not used (HR 1.28, 95% CI 0.82 to 1.98). There is uncertainty of any difference for overall survival (HR 0.89, 95% CI 0.75 to 1.06) and disease-specific survival (HR 0.81, 95% CI 0.57 to 1.13) between those treated with BCG and those in the control groups. Moderate quality evidence from the two meta-analyses by Han & Pan (2006) and Pan *et al.* (2008) both report that drug-related and systemic toxicities are significantly more frequent in the BCG groups than chemotherapy or immunotherapy groups.

TUR + chemotherapy versus TUR alone

One systematic review and meta-analysis of 11 studies and 3,703 patients with primary bladder cancer provides a Peto Odds Ratio (pOR) of 0.56 (95% CI 0.48 to 0.65) for one-year recurrence in favour of adjuvant intravesical chemotherapy compared to TUR alone (Huncharek *et al.*, 2000).

However, significant statistical heterogeneity is reported and sensitivity analyses were conducted. The data were stratified by duration of treatment, which indicates that short-term therapy (≤2 months duration) reduces recurrence at one-year (pOR 0.70, 95% CI 0.55 to 0.90) and two-years (pOR 0.68, 95% CI 0.54 to 0.85) by approximately 30%, as compared to TUR alone (moderate quality evidence). The pooled pOR for five trials where patients received two years of chemotherapy is 0.27 (95% CI 0.19 to 0.39), indicating a 73% reduction in the risk of recurrence at two-years for those treated with chemotherapy.

Moderate quality evidence from one meta-analysis of eight studies and 1,609 patients with recurrent bladder cancer provides a pooled OR for one-year recurrence of 0.62 (95% CI 0.51 to 0.76), in favour of chemotherapy over TUR alone, with no evidence of statistical heterogeneity (Huncharek *et al.*, 2001). For the two- and three-year recurrence rates, significant statistical heterogeneity was reported, which was not accounted for by treatment duration. Therefore, moderate quality evidence is provided from the data when stratified into drug type (adriamycin versus other drugs). The OR for two-year recurrence of studies using adriamycin is 0.57 (95% CI 0.43 to 0.75), with no significant heterogeneity, indicating that drug type was a major contributor to outcome heterogeneity. Drugs other than adriamycin showed a reduction in two-year recurrence of 73% (versus 43% for adriamycin) with an OR of 0.27 (95% CI 0.19 to 0.37).

Another systematic review and meta-analysis provides moderate quality evidence from six randomised trials, which suggests there is uncertainty about the effect of intravesical chemotherapy on progression (HR 1.19, 95% CI 0.97 to 1.47), overall survival (HR 1.1, 95% CI 0.95 to 1.27), and disease-specific survival (HR 1.1, 95% CI not reported but effect size was non-significant), compared to TUR alone (Pawinski *et al.*, 1996).

TUR + one post-operative instillation of chemotherapy versus TUR alone

Low to moderate quality evidence is reported from a systematic review and meta-analysis of 18 trials comparing one post-operative dose of chemotherapy with TUR alone (Abern *et al.*, 2013). 36.6% (577/1576) of those in the TUR + chemotherapy group experienced a recurrence compared with 50.4% (769/1527) of those treated with TUR alone (RR 0.67, 95% CI 0.56 to 0.79), with significant statistical heterogeneity. This corresponds to a number needed to treat of 7.2 patients to avoid one recurrence. Gemcitabine and interferon α-2b does not show a benefit on recurrence, whereas the other chemotherapy agents do. The pooled RR for mitomycin C and epirubicin is 0.71 (95% CI 0.64 to 0.78), in favour of chemotherapy, with no clear dose-response relationship. Funnel plots suggest publication bias with small trials contributing disproportionately to the protective effect of chemotherapy. Progression and survival are not reported. A meta-analysis (Sylvester *et al.*, 2004) of seven trials (1476 patients) reports mild, transient, irritative bladder symptoms including dysuria, frequency and macroscopic haematuria, in approximately 10% of patients treated with one single post-operative dose of intravesical chemotherapy.

TUR+ single dose epirubicin versus TUR + double dose Epirubicin

Low quality evidence from one randomised trial of 143 patients without CIS suggests no difference in recurrence or progression between patients treated with a single dose of 100mg epirubicin within six hours of TUR and those given a second dose of 100mg epirubicin 12-18 hours after TUR (Turkeri *et al.*, 2010).

Moderate quality evidence from one trial of 270 patients without CIS reports that two instillations of 50mg epirubicin within 24 hours of TUR is associated with longer recurrence-free survival than TUR alone (38 months versus 13 months, p=0.004). Recurrence-free survival with two instillations of lower dose epirubicin (20mg/40ml) is not significantly longer than TUR alone (24 months versus 13 months, p=0.163). There are no significant differences between 2x50mg and 2x20mg epirubicin (p=0.146). Local grade one toxicity was reported in 22.9% of the low dose epirubicin group and 35.6% of high dose epirubicin group (RR 0.63, 95% CI 0.39 to 1.02).

Intravesical Adriamycin versus Epirubicin

Moderate quality evidence is provided by two randomised trials comparing one year treatment with adriamycin with the same schedule of epirubicin (Eto *et al.*, 1994; Shuin *et al.*, 1994). There were no differences in recurrence rate (RR 1.31, 95% CI 0.72 to 2.4) or local toxicities (RR 0.73, 95% CI 0.46 to 1.15) between the two treatment arms.

Adjuvant intravesical BCG versus adjuvant intravesical chemotherapy

One systematic review of nine trials and 2,261 patients (Huncharek *et al.*, 2003) reports low quality evidence of an overall OR for one-year recurrence of 0.89 (95% CI 0.74 to 1.07), with significant heterogeneity. Heterogeneity persisted despite stratification by chemotherapy drug type. A sensitivity analysis was therefore performed stratifying by previous intravesical chemotherapy. Pooling all studies that enrolled patients with prior chemotherapy (1480 patients) provides moderate quality evidence, with an OR of 0.54 (95% CI 0.43 to 0.69) in favour of BCG. This reflects a 46% reduction in tumour recurrence at one-year among patients treated with BCG versus chemotherapy, and a lack of statistical heterogeneity. Pooling data from two studies which excluded patients previously treated with chemotherapy gives an OR of 1.82 (95% CI 1.37 to 2.41), in favour of chemotherapy. This suggests that amongst patients not previously treated, intravesical chemotherapy (MMC) reduces tumour recurrence by 82% versus BCG. Similar results were found for two-year and three-year recurrence when stratified by previous therapy.

One systematic review of eight randomised trials and 2,427 patients (Huncharek *et al.*, 2004) randomised to either adjuvant intravesical BCG or chemotherapy provides moderate quality evidence of an OR for progression of 1.24 (95% CI 0.95 to 1.61), in favour of BCG. The confidence intervals include the value of no effect which reflects uncertainty about a difference in progression between the two treatments. The total number of events in each arm is not reported. The pooled OR of the two trials (781 patients) which excluded patients who had previously been treated with intravesical chemotherapy is 0.75 (0.45 to 1.25) in favour of MMC. In trials which included patients previously treated with chemotherapy the OR is 1.49 (1.09 to 2.03) in favour of BCG.

One meta-analysis (Sylvester *et al.*, 2005) of nine randomised trials and 700 patients with CIS provides moderate quality evidence that 34% of complete responders treated with BCG and 50% of complete responders treated with chemotherapy recurred during follow-up (HR 0.47, 95% CI 0.31 to 0.73, in favour of BCG). 47% of patients treated with BCG and 26% treated with chemotherapy had no evidence of disease during follow-up, relating to an absolute difference of 20% and a relative reduction of 59% in the odds of treatment failure on BCG (HR 0.41, 95% CI 0.30 to 0.56). BCG is only superior to MMC in the trials where maintenance BCG was given. Data on progression was less conclusive with a HR of 0.74 (95% CI 0.45 to 1.22). Overall survival is reported in three studies (407

patients). 35.9% of patients treated with chemotherapy and 34.2% treated with BCG therapy died from any cause. Two trials reported disease-specific survival. 13.3% of patients treated with chemotherapy and 10.5% of patients treated with BCG died due to bladder cancer.

BCG versus Mitomycin C (MMC)

Moderate quality evidence is reported from one meta-analysis (Bohle *et al.*, 2003) of 2,749 patients from nine prospective trials and two observational studies. A further trial of 92 patients was indentified and added to the pooled analysis for recurrence (Mangiarotti *et al.*, 2008). The overall RR for recurrence is 0.77 (95% CI 0.63 to 0.95) in favour of BCG over MMC. High quality evidence from a meta-analysis of individual patient data (Malmstrom *et al.*, 2009) including nine trials (2,820 patients) reported that in trials with BCG maintenance, there is a 32% reduction in the risk of recurrence with BCG compared to MMC (HR 0.68, 95% CI 0.58 to 8), whilst there is a 28% risk increase for BCG trials without maintenance (HR 1.28, 95% CI 1.07 to 1.52). Maintenance BCG is more effective than MMC in both patients previously treated and those not previously treated with intravesical chemotherapy.

Moderate quality evidence from one meta-analysis including 1,277 patients (Bohle *et al.*, 2004) reports no difference between BCG and MMC in terms of disease progression (RR 0.79, 95% CI 0.61 to 1.03). However, BCG does show superiority over MMC in the subgroup of BCG maintenance trials (RR 0.70, 95% CI 0.52 to 0.94). Moderate quality evidence from seven trials (1,880 patients) in the IPD meta-analyses reports that after a median follow-up of 4.8 years, 12% of patients progressed and 24% died (of those 30% died from bladder cancer). There are no significant differences between MMC and BCG for these end-points, even when stratified by BCG maintenance and patient risk groups.

Cystitis was more frequent in the BCG group compared to the MMC group (53.8% vs. 39.2%, $p<0.001$). Local and systemic toxicities were more frequent in the BCG group, except for allergy and skin reactions which were more common in MMC group. The risk of cystitis was no different between maintenance BCG and no maintenance BCG. No deaths from sepsis were reported in either arm (Bohle *et al.*, 2003).

BCG versus Epirubicin (EPI)

Moderate quality evidence from one meta-analysis of five randomised trials (Shang *et al.*, 2011), reports that the risk of recurrence was reduced in patients treated with BCG (35.9%) compared to EPI (51.4%) with a RR of 0.69 (95% CI 0.60 to 0.79), in favour of BCG. Low quality evidence from a subgroup analysis demonstrates no significant difference in recurrence between BCG and EPI in two trials using Pasteur strain BCG (RR 0.78, 95% CI 0.56 to 1.10). Low quality evidence for disease progression demonstrated that there are no significant differences between BCG and EPI (RR 0.78, 95% CI 0.54 to 1.13). No differences are reported for overall mortality (two studies) or disease-specific mortality (two studies). However, overall mortality is less frequent in the TICE BCG group compared to the EPI group in the study by Sylvester *et al.* (2010) (RR 0.79, 95% CI 0.62 to 0.99). Drug-induced cystitis (54% versus 32%), haematuria (31% versus 16%), and systemic side-effects (35% versus 1%) are significantly more frequent with BCG than EPI. However, there is significant heterogeneity between trials for systemic side-effects due to the frequency of BCG administration across studies. Moderate quality evidence from four randomised trials suggests there are no

significant differences for delayed or terminated treatment due to adverse events between BCG and EPI (9% versus 7%) (RR 0.91, 95% CI 0.41 to 2.04).

BCG versus Gemcitabine

One systematic review by Jones *et al.* (2012) includes three studies comparing Gemcitabine with BCG. Heterogeneity between trials prevented pooling of data. One trial of 80 patients at intermediate risk of recurrence (primary Ta-T1, no CIS) provides low quality evidence that BCG (no maintenance) and Gemcitabine showed similar rates of recurrence (25% vs. 30%) and progression, with significantly more adverse effects with BCG. Moderate quality evidence is provided by one trial of 64 high risk patients, which reports that recurrence rate is higher for Gemcitabine than BCG (53% vs. 28%) and time to recurrence is shorter with Gemcitabine (25.6 months vs. 39.4 months). No patients in either group had disease progression at a mean follow-up of 44 months. Local and systemic toxicity are similar between groups. In this trial, maintenance therapy for non-recurring patients in each group was up to 36 months duration. No evidence about survival is reported.

Maintenance BCG versus induction BCG

Six trials of maintenance versus induction BCG were indentified which vary in the population included and the schedule and duration of maintenance therapy. High quality evidence from five of these trials reports that 53.9% of patients in the BCG induction arm had a recurrence, compared to 37.6% in the maintenance BCG arm (RR 0.70, 95% CI 0.60 to 0.81). Moderate quality evidence from five trials suggests that there are no overall differences in progression (27.6% versus 31.8%). However, this data should be interpreted with caution due to the variation in BCG maintenance schedules and the duration of follow-up across studies. There are no differences between groups in terms of overall survival and disease-specific survival. Moderate quality evidence from two trials suggests that dysuria is more frequent in the maintenance arm (88.9% versus 68.3%). Rates of fever/chills are not different between groups (RR 1.47, 95% CI 0.88 to 2.44).

One trial reported moderate quality evidence that there are no significant changes in quality of life scores (EORTC-QLQ) in either group from induction treatment to 14 months after randomisation (Koga *et al.*, 2010). Very low quality evidence from one observational study reports that overall quality of life was moderate, and more patients rated it as good during maintenance than during induction therapy (Mack *et al.*, 1996).

Dose of BCG

Low dose versus standard dose BCG

Two trials provide moderate quality evidence of no difference in recurrence, progression, overall survival and disease-specific survival between one-third (27mg) dose and full dose (81mg) BCG. One trial (Martinez-Pineiro *et al.*, 2002) included 500 patients (Ta/T1/CIS, G1-G3) and the other trial (Martinez-Pineiro *et al.*, 2005) included 155 patients with T1G3 disease or CIS. Martinez-Pineiro *et al.* (2002) reports that, in patients with multifocal disease, standard dose BCG is more effective against recurrences and progression than reduced dose BCG. Local toxicity is significantly reduced in the low dose BCG arm (53% versus 67%), and fewer patients have delayed instillations or withdraw from treatment. There are no differences between groups for severe systemic toxicities (3.8% versus 2.7%).

One trial of 80 patients provides low quality evidence of no difference in recurrence, progression or cystitis between patients receiving 81mg BCG versus those receiving 54mg BCG (Yalcinkaya *et al.*, 1998). One trial of 128 patients randomised into three arms, provides low quality evidence of no difference in recurrence rates between 120mg BCG, 80mg BCG and 40mg BCG. No patients had disease progression. Both local toxicity and systemic toxicity were reduced with lower dose of BCG (Agrawal *et al.*, 2007).

Low dose versus very low dose BCG

Moderate quality evidence from one trial (Ojea *et al.*, 2007) suggests that there are no differences in recurrence-free survival between low dose BCG (27mg) and very-low dose BCG (13.5mg) in intermediate risk patients. There are no differences in time to progression and cancer-specific survival between the two BCG treatment groups. Rates of local (65.5% vs. 64.1%) and systemic (11.3% vs. 10.8%) adverse events are also similar between the two groups.

Low dose and standard dose with 1 year or 3 year maintenance

Moderate quality evidence is provided by one trial of 1,355 patients randomised into four trial arms (Oddens *et al.*, 2012). With a median follow-up of 7.1 years, no differences are reported for recurrence, progression, overall survival and toxicity between one-third (27mg) dose and full dose (81mg) BCG. When results are stratified by maintenance and dose, one-third dose BCG with one-year maintenance is suboptimal compared to full-dose BCG with three-year maintenance (HR for disease-free interval 0.75, 95% CI 0.59 to 0.94). In intermediate-risk patients, three years of maintenance is more effective than one year in patients receiving one-third dose (HR 1.35, 95% CI 1.03 to 1.79) but not in patients receiving full-dose (HR 0.88, 95% CI 0.64 to 1.21). In high-risk patients, three years of maintenance is more effective than one year in patients receiving full dose (HR 1.61, 95% CI 1.13 to 2.30) but not in patients receiving one-third dose BCG (HR 1.01, 95% CI 0.69 to 1.47). No significant differences are reported between treatment groups for the time to progression or overall survival.

The schedule and duration of intravesical chemotherapy

One systematic review of randomised trials (Sylvester *et al.*, 2008) which compared intravesical instillations with respect to their number, frequency, timing, duration, dose, or dose intensity concludes that the optimal schedule and duration of intravesical chemotherapy after an immediate instillation remains unknown. In low-risk patients, one immediate instillation of epirubicin may not be less effective than a delayed course of multiple instillations. In patients with multiple tumours, one immediate instillation is insufficient treatment. Additional instillations may further reduce the recurrence rate; however, there is no conclusive evidence regarding their optimal duration. A short intensive schedule of instillations within the first 3–4 months after an immediate instillation may be as effective as longer-term treatment schedules. Instillations during ≥1 year in intermediate-risk patients seem effective only when an immediate instillation has not been given. Higher drug concentrations and optimization of the drug's concentration in the bladder may provide better results.

Chemotherapy + maintenance BCG versus maintenance BCG alone

Low quality evidence is provided by a systematic review of four randomised trials (801 patients) comparing sequential chemotherapy added to maintenance BCG with maintenance BCG alone

(Houghton *et al.*, 2012). A further study of 96 patients with CIS which compared MMC and BCG with BCG alone was also identified and added to the meta-analysis (Oosterlinck *et al.*, 2011). The dose and duration of intravesical therapies used and the average length of follow-up varies across trials. Meta-analysis of five trials provides low quality evidence of uncertainty of a difference in recurrence between the combination arms (42.6%) and the BCG-alone arms (46.7%) (RR 0.92, 95% CI 0.79 to 1.08), but significant heterogeneity (p=0.03). Sub-group analyses provides moderate quality evidence that adding chemotherapy to maintenance BCG was associated with lower recurrence than BCG alone for Ta or T1 disease (RR 0.75, 95% CI 0.61 to 0.92), but not for CIS (RR 1.13, 95% CI 0.93 to 1.37).

Meta-analysis of five trials provides low quality evidence of no significant difference in progression between the combination arms (11.1%) and the BCG-alone arms (13%) (RR 0.84, 95% CI 0.59 to 1.20), but significant heterogeneity (p=0.03). Sub-group analyses provide moderate quality evidence that adding chemotherapy to maintenance BCG is associated with lower progression than BCG alone for Ta or T1 disease (RR 0.45, 95% CI 0.25 to 0.81), but not for CIS (RR 1.33, 95% CI 0.83 to 2.13).

Three studies report drug-related toxicity, with no differences in cystitis, haematuria or fever between groups. The numbers of adverse events in each arm is not reported.

Table 39. GRADE evidence profile: TUR + BCG versus TUR alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR + BCG	TUR alone	Relative (95% CI)	Absolute	
Recurrence at 12 months											
6[1]	randomised trials	none	none	none	serious[2]	none	79/275 (28.7%)	144/257 (56%)	RR 0.54 (0.44 to 0.66)	258 fewer per 1000 (from 191 fewer to 314 fewer)	⊕⊕⊕O MODERATE
Recurrence at 12 months - Medium/high risk patients											
4[1]	randomised trials	none	none	none	serious[2]	none	64/188 (34%)	117/204 (57.4%)	RR 0.59 (0.47 to 0.73)	235 fewer per 1000 (from 155 fewer to 304 fewer)	⊕⊕⊕O MODERATE
Recurrence at 12 months - Medium/high risk but possibly some low risk											
2[1]	randomised trials	none	none	none	serious[2]	none	15/87 (17.2%)	27/53 (50.9%)	RR 0.35 (0.21 to 0.61)	331 fewer per 1000 (from 199 fewer to 402 fewer)	⊕⊕⊕O MODERATE
Recurrence (time-to-event data, follow-up 14 to 36 months)											
6[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	HR 0.44 (0.34 to 0.56)	56% reduction in the risk of recurrence in favour of BCG	⊕⊕⊕O MODERATE
Recurrence - Medium/high risk patients (time-to-event data, follow-up 14 to 36 months)											
4[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	HR 0.46 (0.34 to 0.61)	54% reduction in the risk of recurrence in favour of BCG	⊕⊕⊕O MODERATE
Recurrence - Medium/high risk but possibly some low risk (time-to-event data, follow-up 14 to 36 months)											
2[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	HR 0.37 (0.22 to (0.64)	63% reduction in the risk of recurrence in favour of BCG	⊕⊕⊕O MODERATE
Progression											
0	No evidence										
Overall survival											
0	No evidence										
Disease-specific survival											
0	No evidence										
Treatment-related morbidity											
6[1]	randomised trials	none	none	none	serious[2]	none	-[4]	NR	-	-	⊕⊕⊕O MODERATE
Treatment-related mortality (follow-up 14 to 36 months)											
6[1]	randomised trials	none	none	none	serious[2]	none	0/275 (0%)	0/257 (0%)	-	-	⊕⊕⊕O MODERATE
Health-related quality of life											
0	No evidence										

[1] From meta-analysis in Shelley (2000); [2] Low number of events reduces precision; [3] Number of events not reported in Shelley 2000; [4] Main toxicities associated with BCG: 67% cystitis, 23% haematuria, 25% fever, 71% urinary frequency. No BCG sepsis or deaths reported

Table 40. GRADE evidence profile: TUR + BCG versus TUR + other treatment (chemotherapy or other immunotherapy) or TUR alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR+BCG	TUR+other treatment	Relative (95% CI)	Absolute	
Recurrence											
48[1]	randomised trials & observational studies	none	serious[2]	none	none	none	1900/4952 (38.4%)	2231/4530 (49.2%)	OR 0.59 (0.49 to 0.71)[3]	128 fewer per 1000 (from 85 fewer to 170 fewer)	⊕⊕⊕O MODERATE
Recurrence by BCG maintenance											
8[4]	randomised trials & observational studies	none	none	none	none	none	224/596 (37.6%)	243/474 (51.3%)	RR 0.65 (0.48 to 0.88)[3]	179 fewer per 1000 (from 62 fewer to 267 fewer)	⊕⊕⊕⊕ HIGH
Recurrence by induction BCG only											
10[4]	randomised trials & observational studies	none	serious[2]	none	serious[5]	none	458/963 (47.6%)	570/1109 (51.4%)	RR 0.99 (0.77 to 1.28)[3]	5 fewer per 1000 (from 118 fewer to 144 more)	⊕⊕OO LOW
Recurrence, BCG+TUR vs. TUR alone											
9[4]	randomised trials & observational studies	none	none	none	none	none	230/638 (36.1%)	268/462 (58%)	RR 0.59 (0.45 to 0.78)[3]	238 fewer per 1000 (from 128 fewer to 319 fewer)	⊕⊕⊕⊕ HIGH
Recurrence, BCG vs. Chemotherapy											
10[4]	randomised trials & observational studies	none	serious[2]	none	serious[5]	none	378/910 (41.5%)	398/883 (45.1%)	RR 0.94 (0.77 to 1.14)[3]	27 fewer per 1000 (from 104 fewer to 63 more)	⊕⊕OO LOW
Recurrence, in patients with papillary tumours											
10[4]	randomised trials & observational studies	none	serious[2]	none	none	none	274/653 (42%)	407/718 (56.7%)	RR 0.73 (0.61 to 0.87)[3]	153 fewer per 1000 (from 74 fewer to 221 fewer)	⊕⊕⊕O MODERATE
Progression (follow-up median 2.5 years)											
24[6]	randomised trials	none	none	none	none	none	260/2658 (9.8%)	304/2205 (13.8%)	HR 0.73 (0.6 to 0.88)	35 fewer per 1000 (from 15 fewer to 53 fewer)	⊕⊕⊕⊕ HIGH
Progression in studies of BCG versus MMC											
6[6]	randomised trials	none	none	none	serious[5]	none	79/1074 (7.4%)	76/816 (9.3%)	HR 0.86 (0.62 to 1.2)	12 fewer per 1000 (from 34 fewer to 18 more)	⊕⊕⊕O MODERATE
Overall survival, death due to any cause											
9[6]	randomised trials	none	none	none	serious[5]	none	372/1603 (23.2%)	354/1327 (26.7%)	HR 0.89 (0.75 to 1.06)	25 fewer per 1000 (from 59 fewer to 14 more)	⊕⊕⊕O MODERATE
Disease-specific survival, death due to bladder cancer											
8[6]	randomised trials	none	none	none	serious[5]	none	74/1327 (5.6%)	80/1043 (7.7%)	HR 0.81 (0.57 to 1.13)	14 fewer per 1000 (from 32 fewer to 10 more)	⊕⊕⊕O MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR+BCG	TUR+other treatment	Relative (95% CI)	Absolute	
Treatment-related morbidity - Local toxicity											
25[4]	randomised trials & observational studies	none	none	none	Serious[7]	none	44%	30% (MMC)[8]	-	-	⊕⊕⊕O MODERATE
Treatment-related mortality											
0	No evidence										
Health-related quality of life											
0	No evidence										

[1] From meta-analysis in Pan (2014) –included observational studies in meta-analysis; [2] Significant statistical heterogeneity across studies; [3] Random effects model; [4] From meta-analysis (Han, 2006); [5] Confidence interval includes null value which limits precision of outcome; [6] From meta-analysis in Sylvester (2002); [7] Number of events not reported for treatment-related morbidity [8] BCG-induced local and systemic effects were significantly more frequent in the BCG group than in the chemotherapy/immunotherapy groups (Han 2006; Pan 2008). Overall 44% receiving BCG developed local toxicity compared with 30% receiving MMC (Han, 2006).

Table 41. GRADE evidence profile: TUR + BCG versus TUR + other treatment (chemotherapy or other immunotherapy) of TUR alone for T1G3 bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	No BCG	Relative (95% CI)	Absolute	
Recurrence											
15[1]	randomised trials	none	serious[2]	none	none	none	375/915 (41%)	332/733 (45.3%)	RR 0.73 (0.61 to 0.88)	122 fewer per 1000 (from 54 fewer to 177 fewer)	⊕⊕⊕O MODERATE

[1] From meta-analysis in Pan (2008)

[2] significant statistical heterogeneity across studies

Table 42. GRADE evidence profile: TUR + chemotherapy versus TUR alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR+chemo	TUR alone	Relative (95% CI)	Absolute	
Recurrence - primary cancer (follow-up > 1 year; assessed with: 1-year recurrence rate)											
11[1]	randomised trials	none	serious[2]	none	serious[3]	none	NR	NR	OR 0.56 (0.48 to 0.65)	In favour of intravesical chemotherapy	⊕⊕OO LOW
Recurrence - short-term treatment (assessed with: 1-year recurrence rate)											
2[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.70 (0.55 to 0.90)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - short-term treatment (assessed with: 2-year recurrence rate)											
2[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.68 (0.54 to 0.85)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - long-term treatment (1 year) (assessed with: 1-year recurrence rate)											
3[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.65 (0.46 to 0.80)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - long-term treatment (1 year) (assessed with: 2-year recurrence rate)											
3[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.69 (0.57 to 0.83)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - long-term treatment (2 years) (assessed with: 2 year recurrence rate)											
5[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.27 (0.19 to 0.39)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - recurrent cancer (assessed with: 1-year recurrence rate)											
8[4]	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.62 (0.51 to 0.76)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - recurrent cancer (assessed with: 2-year recurrence)											
8[4]	randomised trials	none	serious[2]	none	serious[3]	none	NR	NR	OR 0.46 (0.33 to 0.63)	In favour of intravesical chemotherapy	⊕⊕OO LOW
Recurrence - adriamycin only (assessed with: 2 year recurrence rate)											
5[4]	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.57 (0.43 to 0.75)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - drugs other than adriamycin (assessed with: 2 year recurrence rate)											
6[4]	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.27 (0.19 to 0.37)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Progression (follow-up median 5.5 years)											
6[5]	randomised trials	none	none	none	serious[6]	none	189/1629 (11.6%)	80/906 (8.8%)	HR 1.19 (0.97 to 1.47)	16 more per 1000 (from 3 fewer to 39 more)	⊕⊕⊕O MODERATE
Overall mortality rate (follow-up median 7.8 years)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR+chemo	TUR alone	Relative (95% CI)	Absolute	
6[5]	randomised trials	none	none	none	serious[6]	none	628/1629 (38.6%)	281/906 (31%)	HR 1.1 (0.95 to 1.27)	25 more per 1000 (from 13 fewer to 66 more)	⊕⊕⊕O MODERATE
Disease-specific mortality rate (follow-up median 7.8 years)											
6[5]	randomised trials	none	none	none	serious[6]	none	229/1629 (14.1%)	93/906 (10.3%)	HR 1.1 (NR)	In favour of TUR alone *(non-significant)*	⊕⊕⊕O MODERATE
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From meta-analysis in Huncharek (2000)
[2] Significant statistical heterogeneity
[3] Number of events/participants in each arm not reported (Huncharek, 2000 and 2001)
[4] From meta-analysis in Huncharek (2001)
[5] From meta-analysis in Pawinski (1996)
[6] Low number of events / 95% confidence intervals include null value

Table 43. GRADE evidence profile: TUR+ one single post-operative chemotherapy instillation versus TUR alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR + single dose chemo	TUR alone	Relative (95% CI)	Absolute	
Recurrence - all studies											
18[1]	randomised trials	none	serious[2]	none	none	reporting bias[3]	577/1576 (36.6%)	769/1527 (50.4%)	RR 0.67 (0.56 to 0.79)	166 fewer per 1000 (from 106 fewer to 222 fewer)	⊕⊕OO LOW
Recurrence - Doxorubicin											
1	randomised trials	none	none	none	serious[4]	none	NR/31	NR/28	RR 0.43 (0.23 to 0.78)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - Epirubicin											
6	randomised trials	none	none	none	serious[4]	none	NR/665	NR/685	RR 0.73 (0.66 to 0.82)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - Gemcitabine											
1	randomised trials	none	none	none	serious[5]	none	NR/124	NR/124	RR 0.90 (0.57 to 1.42)	In favour of intravesical chemotherapy *(non-significant)*	⊕⊕⊕O MODERATE
Recurrence - Interferon alpha 2b											
1	randomised trials	none	none	none	serious[5]	none	NR/66	NR/66	RR 1.05 (0.80 to 1.38)	In favour of intravesical chemotherapy *(non-significant)*	⊕⊕⊕O MODERATE
Recurrence - Mitomycin C											
6	randomised trials	none	none	none	serious[5]	none	NR/412	NR/432	RR 0.66 (0.56 to 0.78)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - Thiotepa											
4	randomised trials	none	none	none	serious[4]	none	NR/197	NR/207	RR 0.76 (0.62 to 0.93)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Recurrence - Pirarubicin											
1	randomised trials	none	none	none	serious[4]	none	NR/81	NR/79	RR 0.40 (0.23 to 0.69)	In favour of intravesical chemotherapy	⊕⊕⊕O MODERATE
Progression											
0	No evidence available										
Disease-specific survival											
0	No evidence										

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR + single dose chemo	TUR alone	Relative (95% CI)	Absolute	
	available										
Overall survival											
0	No evidence available										
Treatment-related morbidity											
1[6]	randomised trials	serious[7]	none	none	none	none	10% mild bladder symptoms	NR	-	-	⊕⊕⊕O MODERATE
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From meta-analysis in Abern (2013)

[2] Significant statistical heterogeneity

[3] Funnel plots suggested existence of publication bias, suggesting that small trials in the analysis disproportionately contribute to the protective effect of intravesical chemotherapy.

[4] Small sample size/ low number of events limits precision. Number of events not reported for the analysis stratified by chemotherapy.

[5] Low number of events / confidence intervals include null value

[6] From meta-analysis of 7 trials by Sylvester (2004)

[7] Number of studies reporting toxicity and number of events for symptoms not reported. Adverse effects of TUR alone not reported. Mild, transient, irritating bladder symptoms including dysuria, frequency and macroscopic haematuria, in approximately 10% of patients.

Table 44. GRADE evidence profile: TUR + single dose epirubicin (100mg) versus TUR + double dose epirubicin (2x100mg)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single-dose EPI (100mg)	Double-dose EPI (200mg)	Relative (95% CI)	Absolute	
Recurrence (follow-up 16.9 months)											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	10/68 (14.7%)	16/75 (21.3%)	RR 0.69 (0.34 to 1.41)	66 fewer per 1000 (from 141 fewer to 87 more)	⊕⊕OO LOW
Progression (follow-up 16.9 months)											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	2/68 (2.9%)	6/75 (8%)	RR 0.37 (0.08 to 1.76)	50 fewer per 1000 (from 74 fewer to 61 more)	⊕⊕OO LOW
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Turkeri 2010

[2] Method of randomisation, allocation concealment and blinding not reported. Power analyses not reported. No information provided about excluded patients with insufficient follow-up.

[3] Low number of events / confidence interval includes null value

Table 45. GRADE evidence profile: TUR + 2x20mg/40ml epirubicin versus TUR + 2x50mg/100ml epirubicin versus TUR only

Quality assessment							No of patients			Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A 2x20mg EPI	B 2x50mg EPI	C TUR only	Relative (95% CI)	Absolute	
Recurrence (time-to-event data, follow-up median 44 months)												
1[1]	randomised trials	none	none	none	serious[2]	none	24 mo (n=89)	38 mo (n=90)	13 mo (n=91)	A v B, p=0.194 A v C, p=0.245 B v C, p=0.01	In favour of 2x50mg epirubicin over TUR alone	⊕⊕⊕O MODERATE
Progression												
0	No evidence available											
Overall survival												
0	No evidence available											
Disease-specific survival												
0	No evidence available											
Treatment-related mortality												
0	No evidence available											
Local toxicity - Grade 1												
1[1]	randomised trials	none	none	none	serious[3]	none	20/89 (22.5%)	32/90 (35.6%)	NR	RR 0.63 (0.39 to 1.02)	132 fewer per 1000 (from 217 fewer to 7 more)	⊕⊕⊕O MODERATE
Systemic adverse events												
1[1]	randomised trials	none	none	none	serious[3]	none	4/89 (4.5%)	6/90 (6.7%)	NR	RR 0.67 (0.2 to 2.31)	22 fewer per 1000 (from 53 fewer to 87 more)	⊕⊕⊕O MODERATE
Health-related quality of life												
0	No evidence available											

[1] Saika 2010

[2] Number of events in each arm not reported

[3] Low number of events / confidence interval includes null value

Table 46. GRADE evidence profile: Adriamycin versus Epirubicin

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADR	EPI	Relative (95% CI)	Absolute	
Recurrence											
2[1]	randomised trials	none	none	none	serious[2]	none	19/87 (21.8%)	15/92 (16.3%)	RR 1.31 (0.72 to 2.4)	51 more per 1000 (from 46 fewer to 228 more)	⊕⊕⊕O MODERATE
Local side effects											
2[1]	randomised trials	none	none	none	serious[2]	none	22/87 (25.3%)	32/92 (34.8%)	RR 0.73 (0.46 to 1.15)	94 fewer per 1000 (from 188 fewer to 52 more)	⊕⊕⊕O MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Eto 1994; Shuin 1994

[2] Low number of events / confidence interval includes null value

Table 47. GRADE evidence profile: TUR + chemotherapy versus TUR + BCG

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	Chemotherapy	Relative (95% CI)	Absolute	
Recurrence (follow-up 28-86 months; assessed with: 1-year recurrence)											
9[1]	randomised trials	none	serious[2]	none	serious[3]	none	NR	NR	OR 0.89 (0.74 to 1.07)	In favour of BCG *(non-significant)*	⊕⊕OO LOW
Recurrence - prior chemotherapy (assessed with: 1-year recurrence)											
7	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.54 (0.43 to 0.69)	In favour of BCG	⊕⊕⊕O MODERATE
Recurrence - no prior chemotherapy (assessed with: 1-year recurrence)											
2	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 1.82 (1.37 to 2.41)	In favour of chemotherapy	⊕⊕⊕O MODERATE
Recurrence - prior chemotherapy (assessed with: 3-year recurrence)											
7	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.43 (0.34 to 0.55)	In favour of BCG	⊕⊕⊕O MODERATE
Recurrence - no prior chemotherapy (assessed with: 2-year recurrence)											
2	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 1.67 (1.29 to 2.17)	In favour of chemotherapy	⊕⊕⊕O MODERATE
Progression											
8[4]	randomised trials	none	none	none	serious[5]	none	NR	NR	OR 1.24 (0.95 to 1.61)	In favour of chemotherapy *(non-significant)*	⊕⊕⊕O MODERATE
Progression - prior chemotherapy											
6	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 1.49 (1.09 to 2.03)	In favour of chemotherapy	⊕⊕⊕O MODERATE
Progression - no prior chemotherapy											
2	randomised trials	none	none	none	serious[5]	none	NR	NR	OR 0.75 (0.45 to 1.25)	In favour of BCG *(non-significant)*	⊕⊕⊕O MODERATE
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From meta-analysis in Huncharek 2003; [2] Significant statistical heterogeneity; [3] Number of patients/events in each arm not reported in Huncharek 2003 and 2004; From meta-analyses in Huncharek 2004; [5] Number of patients and events not reported. Confidence interval includes null value

Table 48. GRADE evidence profile: TUR + chemotherapy versus TUR + BCG for CIS only

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	Chemotherapy	Relative (95% CI)	Absolute	
Recurrence in complete responders (follow-up median 3.6 years)											
7[1]	randomised trials	none	none	none	serious[2]	none	69/203 (34%)	79/158 (50%)	HR 0.48 (0.31 to 0.74)	217 fewer per 1000 (from 99 fewer to 307 fewer)	⊕⊕⊕O MODERATE
No evidence of disease (follow-up median 3.6 years)											
9	randomised trials	none	none	none	serious[2]	none	161/345 (46.7%)	93/355 (26.2%)	HR 0.41 (0.3 to 0.56)	145 fewer per 1000 (from 106 fewer to 175 fewer)	⊕⊕⊕O MODERATE
Disease-free in studies with MMC according to BCG maintenance (follow-up median 3.6 years)											
5	randomised trials	none	none	none	serious[2,3]	none	78/170 (45.9%)	63/177 (35.6%)	HR 0.7 (0.44 to 1.09)	91 fewer per 1000 (from 180 fewer to 25 more)	⊕⊕⊕O MODERATE
Disease-free in studies with MMC according to BCG maintenance - No BCG maintenance											
2	randomised trials	none	none	none	serious[2,3]	none	29/62 (46.8%)	14/28 (50%)	HR 1.24 (0.5 to 3.06)	77 more per 1000 (from 207 fewer to 380 more)	⊕⊕⊕O MODERATE
Disease-free in studies with MMC according to BCG maintenance - BCG maintenance											
3	randomised trials	none	none	none	serious[2]	none	49/108 (45.4%)	49/149 (32.9%)	HR 0.58 (0.34 to 0.97)	122 fewer per 1000 (from 8 fewer to 202 fewer)	⊕⊕⊕O MODERATE
Progression											
6	randomised trials	none	none	none	serious[2,3]	none	47/240 (19.6%)	36/234 (15.4%)	HR 0.74 (0.45 to 1.21)	35 fewer per 1000 (from 78 fewer to 26 more)	⊕⊕⊕O MODERATE
Overall mortality rate (follow-up median 3.6 years)											
3	randomised trials	none	none	none	serious[2]	none	63/184 (34.2%)	80/223 (35.9%)	NR	-	⊕⊕⊕O MODERATE
Disease-specific mortality rate											
2	randomised trials	none	none	none	serious[2]	none	11/105 (10.5%)	14/105 (13.3%)	NR	-	⊕⊕⊕O MODERATE
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From meta-analysis in Sylvester 2005; [2] Low number of events limits precision; [3] Confidence interval includes null value

Table 49. GRADE evidence profile: BCG versus MMC

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	MMC	Relative (95% CI)	Absolute	
Recurrence (follow-up median 26 months)											
12[1]	randomised trials	none	serious[2]	none	none	none	571/1467 (38.9%)	639/1374 (46.5%)	RR 0.77 (0.63 to 0.95)	107 fewer per 1000 (from 23 fewer to 172 fewer)	⊕⊕⊕O MODERATE
Recurrence - No BCG maintenance											
5[1]	randomised trials	none	serious[2]	none	serious[4]	none	261/640 (40.8%)	201/557 (36.1%)	RR 0.95 (0.72 to 1.25)	18 fewer per 1000 (from 101 fewer to 90 more)	⊕⊕OO LOW
Recurrence - BCG maintenance											
7[1]	randomised trials	none	serious[2]	none	none	none	287/781 (37.5%)	438/817 (53.6%)	RR 0.68 (0.55 to 0.83)	172 fewer per 1000 (from 91 fewer to 241 fewer)	⊕⊕⊕O MODERATE
Recurrence by risk and maintenance - Maintenance and high risk											
3[1]	randomised trials	none	serious[2]	none	none	none	144/352 (40.9%)	200/352 (56.8%)	RR 0.69 (0.5 to 0.96)	176 fewer per 1000 (from 23 fewer to 284 fewer)	⊕⊕⊕O MODERATE
Recurrence by risk and maintenance - Maintenance and intermediate risk											
3[1]	randomised trials	none	none	none	none	none	143/429 (33.3%)	215/419 (51.3%)	RR 0.59 (0.48 to 0.73)	210 fewer per 1000 (from 139 fewer to 267 fewer)	⊕⊕⊕⊕ HIGH
Recurrence by risk and maintenance - No maintenance and high risk											
1[1]	randomised trials	none	none	none	serious[3,4]	none	19/31 (61.3%)	24/30 (80%)	RR 0.77 (0.55 to 1.07)	184 fewer per 1000 (from 360 fewer to 56 more)	⊕⊕⊕O MODERATE
Recurrence by risk and maintenance - No maintenance and intermediate risk											
4[1]	randomised trials	none	serious[2]	none	serious[4]	none	242/609 (39.7%)	177/527 (33.6%)	RR 1.01 (0.75 to 1.37)	3 more per 1000 (from 84 fewer to 124 more)	⊕⊕OO LOW
Progression (follow-up median 26 months)											
9[5]	randomised trials	none	none	none	serious[3,4]	none	98/1277 (7.7%)	107/1133 (9.4%)	RR 0.79 (0.61 to 1.03)	20 fewer per 1000 (from 37 fewer to 3 more)	⊕⊕⊕O MODERATE
Progression - No BCG Maintenance											
4[5]	randomised trials	none	none	none	serious[3,4]	none	30/609 (4.9%)	21/527 (4%)	RR 1.15 (0.67 to 2)	6 more per 1000 (from 13 fewer to 40 more)	⊕⊕⊕O MODERATE
Progression - BCG maintenance											
5[5]	randomised trials	none	none	none	serious[3]	none	68/668 (10.2%)	86/606 (14.2%)	RR 0.7 (0.52 to 0.94)	43 fewer per 1000 (from 9 fewer to 68 fewer)	⊕⊕⊕O MODERATE
Time to first recurrence (Malmstrom IPD) (follow-up median 4.4 years)											
9[6]	randomised trials	none	serious[2]	none	serious[4]	none	616/1437 (42.9%)	600/1383 (43.4%)	HR 0.91 (0.81 to 1.02)	30 fewer per 1000 (from 65 fewer to 6 more)	⊕⊕OO LOW
Time to first recurrence - No BCG maintenance											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	MMC	Relative (95% CI)	Absolute	
4[6]	randomised trials	none	none	none	none	none	309/726 (42.6%)	245/770 (31.8%)	HR 1.28 (1.07 to 1.52)	69 more per 1000 (from 18 more to 123 more)	⊕⊕⊕⊕ HIGH
Time to first recurrence - BCG maintenance											
5[6]	randomised trials	none	none	none	none	none	307/711 (43.2%)	355/613 (57.9%)	HR 0.68 (0.58 to 0.8)	134 fewer per 1000 (from 80 fewer to 184 fewer)	⊕⊕⊕⊕ HIGH
Progression (Malmstrom IPD) (follow-up median 4.8 years)											
7[6]	randomised trials	none	none	none	serious[3,4]	none	114/1050 (10.9%)	110/830 (13.3%)	RR 0.82 (0.64 to 1.05)	24 fewer per 1000 (from 48 fewer to 7 more)	⊕⊕⊕O MODERATE
Overall mortality rate (follow-up median 4.8 years)											
7[6]	randomised trials	none	none	none	serious[4]	none	213/1437 (14.8%)	234/1383 (16.9%)	RR 0.88 (0.74 to 1.04)	20 fewer per 1000 (from 44 fewer to 7 more)	⊕⊕⊕O MODERATE
Disease-specific mortality rate (follow-up median 4.8 years)											
7[6]	randomised trials	none	none	none	serious[3,4]	none	59/1437 (4.1%)	77/1383 (5.6%)	RR 0.74 (0.53 to 1.03)	14 fewer per 1000 (from 27 fewer to 2 more)	⊕⊕⊕O MODERATE
Treatment-related morbidity (assessed with: Rate of cystitis)											
5[1]	randomised trials	none	none	none	none	none	485/901 (53.8%)	304/776 (39.2%)	RR 1.37 (1.25 to 1.5)	145 more per 1000 (from 98 more to 196 more)	⊕⊕⊕⊕ HIGH
Treatment-related morbidity (assessed with: Rate of fever)											
2[1]	randomised trials	none	none	none	serious[3]	none	56/324 (17.3%)	11/332 (3.3%)	RR 5.20 (2.78 to 9.74)	139 more per 1000 (from 59 more to 290 more)	⊕⊕⊕O MODERATE
Treatment-related mortality (assessed with: Sepsis, death)											
5[1]	randomised trials	none	none	none	serious[3]	none	0/901 (0%)	0/776 (0%)	-	-	⊕⊕⊕O MODERATE
Health-related quality of life											
0	No evidence										

[1] From meta-analyses in Bohle (2003); [2] Significant statistical heterogeneity; [3] Small number of events limits precision; [4] Confidence intervals include null value; [5] From meta-analysis in Bohle 2004
[6] From meta-analysis in Malmstrom 2009

Table 50. GRADE evidence profile: BCG versus Epirubicin

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	Epirubicin	Relative (95% CI)	Absolute	
Recurrence (follow-up 33 to 110 months)											
5[1]	randomised trials	serious[2]	none	none	none	none	195/549 (35.5%)	289/562 (51.4%)	RR 0.69 (0.6 to 0.79)	159 fewer per 1000 (from 108 fewer to 206 fewer)	⊕⊕⊕O MODERATE
Recurrence - Connaught BCG											
1	randomised trials	serious[2]	none	none	serious[3]	none	30/102 (29.4%)	59/107 (55.1%)	RR 0.53 (0.38 to 0.75)	259 fewer per 1000 (from 138 fewer to 342 fewer)	⊕⊕OO LOW
Recurrence - Pasteur BCG											
2	randomised trials	serious[2]	none	none	serious[3,4]	none	36/108 (33.3%)	49/115 (42.6%)	RR 0.78 (0.56 to 1.1)	94 fewer per 1000 (from 187 fewer to 43 more)	⊕⊕OO LOW
Recurrence - Tice BCG											
2	randomised trials	none	none	none	none	none	129/339 (38.1%)	181/340 (53.2%)	RR 0.72 (0.6 to 0.85)	149 fewer per 1000 (from 80 fewer to 213 fewer)	⊕⊕⊕⊕ HIGH
Progression											
5	randomised trials	serious[2]	none	none	serious[3,4]	none	44/549 (8%)	58/562 (10.3%)	RR 0.78 (0.54 to 1.13)	23 fewer per 1000 (from 47 fewer to 13 more)	⊕⊕OO LOW
Overall mortality (follow-up 3 to 127 months)											
2	randomised trials	none	none	none	serious[3,4]	none	125/383 (32.6%)	147/386 (38.1%)	RR 0.86 (0.71 to 1.04)	53 fewer per 1000 (from 110 fewer to 15 more)	⊕⊕⊕O MODERATE
Disease-specific mortality											
2	randomised trials	none	serious[5]	none	serious[3,4]	none	22/383 (5.7%)	26/386 (6.7%)	RR 0.94 (0.23 to 3.8)	4 fewer per 1000 (from 52 fewer to 189 more)	⊕⊕OO LOW
Local adverse effects, Drug induced cystitis											
4	randomised trials	none	serious[5]	none	none	none	232/429 (54.1%)	140/441 (31.7%)	RR 1.92 (1.38 to 2.65)	292 more per 1000 (from 121 more to 524 more)	⊕⊕⊕O MODERATE
Local adverse effects, Haematuria											
4	randomised trials	none	none	none	serious[3]	none	132/429 (30.8%)	71/440 (16.1%)	RR 1.9 (1.47 to 2.45)	145 more per 1000 (from 76 more to 234 more)	⊕⊕⊕O MODERATE
Systemic adverse events											
3	randomised trials	none	serious[5]	none	serious[3]	none	134/385 (34.8%)	5/393 (1.3%)	RR 18.01 (2.25 to 143.91)	216 more per 1000 (from 16 more to 1000 more)	⊕⊕OO LOW
Delayed or terminated treatment due to adverse effects											
4	randomised trials	none	none	none	serious[3,4]	none	40/431 (9.3%)	33/441 (7.5%)	RR 0.91 (0.41 to 2.04)	7 fewer per 1000 (from 44 fewer to 78 more)	⊕⊕⊕O MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	Epirubicin	Relative (95% CI)	Absolute	
Treatment-related mortality											
0	No evidence										
Health-related quality of life											
0	No evidence										

[1] From meta-analysis in Shang 2011; [2] Three trials were quasi-randomised by date of birth. Only Sylvester 2010 used good allocation concealment methods. The other 4 trials did not provide information on randomisation and allocation concealment; [3] Small number of events limits precision; [4] Confidence interval includes null value; [5] Statistical heterogeneity between studies

Table 51. GRADE evidence profile: BCG versus Gemcitabine

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	GEM	Relative (95% CI)	Absolute	
Recurrence - intermediate risk (follow-up mean 10.8 months)											
1[1]	randomised trials	serious[2]	none	none	serious[3,4]	none	12/40 (30%)	10/40 (25%)	RR 1.2 (0.59 to 2.45)	50 more per 1000 (from 103 fewer to 363 more)	⊕⊕OO LOW
Progression - intermediate risk (follow-up mean 10.8 months)											
1[1]	randomised trials	serious[2]	none	none	serious[5]	none	NR	NR	No significant difference	-	⊕⊕OO LOW
Toxicity - Dysuria											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	14/40 (35%)	5/40 (12.5%)	RR 2.8 (1.11 to 7.04)	225 more per 1000 (from 14 more to 755 more)	⊕⊕OO LOW
Toxicity - Urinary frequency											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	18/40 (45%)	4/40 (10%)	RR 4.5 (1.67 to 12.12)	350 more per 1000 (from 67 more to 1000 more)	⊕⊕OO LOW
Recurrence - high risk (follow-up mean 44 months)											
1[6]	randomised trials	none	none	none	serious[3,4]	none	9/32 (28.1%)	17/32 (53.1%)	RR 0.53 (0.28 to 1.01)	250 fewer per 1000 (from 382 fewer to 5 more)	⊕⊕⊕O MODERATE
Progression - high risk (follow-up mean 44 months)											
1[6]	randomised trials	none	none	none	serious[3]	none	0/32 (0%)	0/32 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Local toxicity - cystitis											
1[6]	randomised trials	none	none	none	serious[3,4]	none	4/32 (12.5%)	3/32 (9.4%)	RR 1.33 (0.32 to 5.49)	31 more per 1000 (from 64 fewer to 421 more)	⊕⊕⊕O MODERATE
Systemic toxicity - fever											
1[6]	randomised trials	none	none	none	serious[3,4]	none	2/32 (6.3%)	0/32 (0%)	RR 5 (0.25 to 100.21)	-	⊕⊕⊕O MODERATE
Overall survival											
0	No evidence										
Disease-specific survival											
0	No evidence										
Treatment-related mortality											
0	No evidence										
Health-related quality of life											
0	No evidence										

[1] Bendary 2011; [2] Randomisation method not reported. No blinding of intervention or outcome assessment. Short follow-up; [3] Small number of events; [4] Confidence interval includes null value
[5] Number of events not reported - likely to be low number; [6] Porena 2010

Table 52. GRADE evidence profile: Maintenance BCG versus induction BCG

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Maintenance BCG	Induction BCG	Relative (95% CI)	Absolute	
Recurrence (follow-up 16 to 84 months)											
5[1]	randomised trials	none	none	none	none	none	129/343 (37.6%)	185/343 (53.9%)	RR 0.7 (0.6 to 0.81)	162 fewer per 1000 (from 102 fewer to 216 fewer)	⊕⊕⊕⊕ HIGH
Progression											
5[2]	randomised trials	none	none	none	serious[3]	none	102/369 (27.6%)	117/368 (31.8%)	RR 0.87 (0.71 to 1.06)	41 fewer per 1000 (from 92 fewer to 19 more)	⊕⊕⊕O MODERATE
Overall mortality											
3[4]	randomised trials	none	none	none	serious[3]	none	94/281 (33.5%)	103/280 (36.8%)	RR 0.91 (0.73 to 1.13)	33 fewer per 1000 (from 99 fewer to 48 more)	⊕⊕⊕O MODERATE
Disease-specific mortality											
2[5]	randomised trials	none	none	none	serious[3]	none	3/89 (3.4%)	3/88 (3.4%)	RR 0.99 (0.23 to 4.3)	0 fewer per 1000 (from 26 fewer to 113 more)	⊕⊕⊕O MODERATE
Treatment-related morbidity - dysuria											
2[6]	randomised trials	none	none	none	serious[7]	none	56/63 (88.9%)	43/63 (68.3%)	RR 1.3 (1.08 to 1.57)	205 more per 1000 (from 55 more to 389 more)	⊕⊕⊕O MODERATE
Treatment-related morbidity - fever/chills											
2[6]	randomised trials	none	none	none	serious[7]	none	25/63 (39.7%)	17/63 (27%)	RR 1.47 (0.88 to 2.44)	127 more per 1000 (from 32 fewer to 389 more)	⊕⊕⊕O MODERATE
Treatment-related mortality											
1[8]	randomised trials	none	none	none	serious[3]	none	2/192 (1%)	0/192 (0%)	RR 5 (0.24 to 103.47)	-	⊕⊕⊕O MODERATE
Health-related quality of life (measured with: EORTC QLQ-C30)											
1[9]	randomised trials	none	none	none	serious[10]	none	No change in QoL	No change in QoL	-		⊕⊕⊕O MODERATE
Health-related quality of life (assessed with: Proportion of patients with good overall Quality of life)											
1[11]	observational studies	none	none	none	serious[10]	none	48%	15%	-	-	⊕OOO VERY LOW

[1] Hudson 1987; Lamm 2000; Palou 2007; Hinotsu 2010; Koga 2010; [2] Badalament 1987; Hinotsu 2010; Koga 2010; Palou 2007; Lamm 2000; [3] Low number of events/ confidence interval includes null value; [4] Koga 2010; Lamm 2000; Palou 2007; [5] Koga 2010; Palou 2007; [6] Hinotsu 2010; Hudson 1987; [7] Low number of events; [8] Lamm 2000; [9] Koga 2010; [10] Small sample size; [11] Mack 1996

Table 53. GRADE evidence profile: Standard dose BCG (81mg) versus reduced dose BCG (27mg)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	81mg BCG	27mg BCG	Relative (95% CI)	Absolute	
Recurrence (follow-up median 65 months)											
2[1]	randomised trials	none	none	none	serious[2,3]	none	103/334 (30.8%)	109/320 (34.1%)	RR 0.9 (0.72 to 1.12)	34 fewer per 1000 (from 95 fewer to 41 more)	⊕⊕⊕O MODERATE
Progression (follow-up median 65 months)											
2[1]	randomised trials	none	none	none	serious[2,3]	none	49/334 (14.7%)	52/320 (16.3%)	RR 0.89 (0.62 to 1.27)	18 fewer per 1000 (from 62 fewer to 44 more)	⊕⊕⊕O MODERATE
Overall mortality											
2[1]	randomised trials	none	none	none	serious[2,3]	none	75/334 (22.5%)	76/320 (23.8%)	RR 0.94 (0.71 to 1.24)	14 fewer per 1000 (from 69 fewer to 57 more)	⊕⊕⊕O MODERATE
Disease-specific mortality											
2[1]	randomised trials	none	none	none	serious[2,3]	none	30/334 (9%)	29/320 (9.1%)	RR 0.98 (0.6 to 1.59)	2 fewer per 1000 (from 36 fewer to 53 more)	⊕⊕⊕O MODERATE
Treatment-related mortality											
2[1]	randomised trials	none	none	none	serious[2]	none	0/334 (0%)	0/320 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Any grade local toxicity											
2[1]	randomised trials	none	none	none	none	none	225/334 (67.4%)	170/320 (53.1%)	RR 1.27 (1.12 to 1.44)	143 more per 1000 (from 64 more to 234 more)	⊕⊕⊕⊕ HIGH
Grade 3-4 Local toxicity											
2[1]	randomised trials	none	none	none	serious[2]	none	60/334 (18%)	24/320 (7.5%)	RR 2.38 (1.52 to 3.72)	104 more per 1000 (from 39 more to 204 more)	⊕⊕⊕O MODERATE
Any grade systemic toxicity											
2[1]	randomised trials	none	none	none	serious[2]	none	93/334 (27.8%)	42/320 (13.1%)	RR 2.15 (1.55 to 2.98)	151 more per 1000 (from 72 more to 260 more)	⊕⊕⊕O MODERATE
Grade 3-4 systemic toxicity											
2[1]	randomised trials	none	none	none	serious[2,3]	none	9/334 (2.7%)	12/320 (3.8%)	RR 0.74 (0.32 to 1.69)	10 fewer per 1000 (from 26 fewer to 26 more)	⊕⊕⊕O MODERATE
Health-related quality of life											
0	No evidence available										

[1] Martinez-Pineiro 2002; 2005; [2] Low number of events limits precision; [3] Confidence interval includes null value

Table 54. GRADE evidence profile: Low dose BCG (27mg) versus very low dose BCG (13.5mg)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	27mg BCG	13.5mg BCG	Relative (95% CI)	Absolute	
Recurrence (follow-up 0-114 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	38/142 (26.8%)	50/139 (36%)	RR 0.74 (0.52 to 1.06)	94 fewer per 1000 (from 173 fewer to 22 more)	⊕⊕⊕O MODERATE
Progression (follow-up 0-114 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	14/142 (9.9%)	18/139 (12.9%)	RR 0.76 (0.39 to 1.47)	31 fewer per 1000 (from 79 fewer to 61 more)	⊕⊕⊕O MODERATE
Cancer-specific mortality (follow-up 0-114 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	3/142 (2.1%)	5/139 (3.6%)	RR 0.59 (0.14 to 2.41)	15 fewer per 1000 (from 31 fewer to 51 more)	⊕⊕⊕O MODERATE
Overall mortality (follow-up 0-114 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	13/142 (9.2%)	17/139 (12.2%)	RR 0.75 (0.38 to 1.48)	31 fewer per 1000 (from 76 fewer to 59 more)	⊕⊕⊕O MODERATE
Grade 3-4 Local toxicity											
1[1]	randomised trials	none	none	none	serious[2,3]	none	20/142 (14.1%)	10/139 (7.2%)	RR 1.96 (0.95 to 4.03)	69 more per 1000 (from 4 fewer to 218 more)	⊕⊕⊕O MODERATE
Grade 3-4 systemic toxicity											
1[1]	randomised trials	none	none	none	serious[2,3]	none	5/142 (3.5%)	3/139 (2.2%)	RR 1.63 (0.4 to 6.7)	14 more per 1000 (from 13 fewer to 123 more)	⊕⊕⊕O MODERATE
Any grade local toxicity											
1[1]	randomised trials	none	none	none	serious[2,3]	none	93/142 (65.5%)	89/139 (64%)	RR 1.02 (0.86 to 1.22)	13 more per 1000 (from 90 fewer to 141 more)	⊕⊕⊕O MODERATE
Any grade systemic toxicity											
1[1]	randomised trials	none	none	none	serious[2,3]	none	16/142 (11.3%)	15/139 (10.8%)	RR 1.04 (0.54 to 2.03)	4 more per 1000 (from 50 fewer to 111 more)	⊕⊕⊕O MODERATE
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Ojea 2007; [2] Low number of events; [3] Confidence interval includes null value

Table 55. GRADE evidence profile: Standard dose BCG (81mg) versus reduced dose BCG (27mg)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	81mg BCG	27mg BCG	Relative (95% CI)	Absolute	
Recurrence (follow-up median 7.1 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	276/677 (40.8%)	311/678 (45.9%)	RR 0.89 (0.79 to 1.00)	50 fewer per 1000 (from 96 fewer to 0 more)	⊕⊕⊕O MODERATE
Progression (follow-up median 7.1 years)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	53/677 (7.8%)	56/678 (8.3%)	RR 0.95 (0.66 to 1.36)	4 fewer per 1000 (from 28 fewer to 30 more)	⊕⊕⊕O MODERATE
Overall mortality rate (follow-up median 7.1 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	185/677 (27.3%)	184/678 (27.1%)	RR 1.01 (0.85 to 1.20)	3 more per 1000 (from 41 fewer to 54 more)	⊕⊕⊕O MODERATE
Disease-specific mortality rate (follow-up median 7.1 years)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	38/377 (10.1%)	30/678 (4.4%)	RR 1.27 (0.80 to 2.02)	12 more per 1000 (from 9 fewer to 45 more)	⊕⊕⊕O MODERATE
Local or systemic adverse events											
1[1]	randomised trials	none	none	none	serious[2,3]	none	50/657 (7.6%)	53/659 (8%)	RR 0.95 (0.65 to 1.37)	4 fewer per 1000 (from 28 fewer to 30 more)	⊕⊕⊕O MODERATE
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Oddens 2012

[2] Confidence interval includes null value

[3] Low number of events

Table 56. GRADE evidence profile: Standard dose BCG (81mg) versus reduced dose BCG (54mg)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	81mg BCG	54mg BCG	Relative (95% CI)	Absolute	
Recurrence (follow-up mean 33.5 months)											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	9/40 (22.5%)	16/40 (40%)	RR 0.56 (0.28 to 1.12)	176 fewer per 1000 (from 288 fewer to 48 more)	⊕⊕OO LOW
Progression (follow-up mean 33.5 months)											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	1/40 (2.5%)	2/40 (5%)	RR 0.5 (0.05 to 5.3)	25 fewer per 1000 (from 47 fewer to 215 more)	⊕⊕OO LOW
Treatment-related morbidity: Cystitis											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	24/40 (60%)	19/40 (47.5%)	RR 1.26 (0.84 to 1.91)	123 more per 1000 (from 76 fewer to 432 more)	⊕⊕OO LOW
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Yalcinkaya 1998

[2] No details of randomisation method, allocation concealment, or blinding. Method and results of data analysis not reported.

[3] Small number of events / confidence intervals include null value

Table 57. GRADE evidence profile: 120mg BCG versus 80mg BCG versus 40mg BCG

Quality assessment							No of patients			Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A: 120mg BCG	B: 80mg BCG	C: 40mg BCG	Relative (95% CI)	Absolute	
Recurrence (follow-up mean 36 months)												
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	8/40 (20%)	12/48 (25%)	8/40 (20%)	A versus B – RR 0.80 (0.36 to 1.76) A versus C – RR 1.00 (0.42 to 2.40) B versus C – RR 1.25 (0.57 to 2.75)	-	⊕⊕OO LOW
Progression (follow-up mean 36 months)												
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	0/40 (0%)	0/48 (0%)	0/40 (0%)	-	-	⊕⊕OO LOW
Overall survival												
0	No evidence available											
Disease-specific survival												
0	No evidence available											
Treatment-related mortality												
0	No evidence available											
Local toxicity - Dysuria (follow-up mean 36 months)												
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	28/40 (70%)	16/48 (33.3%)	12/40 (30%)	A versus B – RR 2.10 (1.34 to 3.29) A versus C – RR 2.33 (1.39 to 3.91) B versus C – RR 1.11 (0.60 to 2.07)	-	⊕⊕OO LOW
Systemic toxicity - Fever >38 C (follow-up mean 36 months)												
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	12/40 (30%)	0/48 (0%)	0/40 (0%)	A versus B – RR 29.88 (1.82 to 489.42) A versus C – RR 25 (1.53 to 408.39)	-	⊕⊕OO LOW
Health-related quality of life												
0	No evidence available											

[1] Agrawal 2007; [2] Method of randomisation, allocation concealment not reported. Baseline characteristics of patients not reported; [3] Low number of events limits precision

Table 58. GRADE evidence profile: One immediate instillation chemotherapy versus one instillation plus maintenance

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	One dose	One dose + maintenance	Relative (95% CI)	Absolute	
Recurrence											
3[1]	randomised trials	serious[2]	none	none	none	none	179/446 (40.1%)	138/433 (31.9%)	Not pooled	-	⊕⊕⊕O MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity (assessed with: Treatment stopped due to severe cystitis)											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life (measured with: SF-36)											
0	No evidence available										

[1] From systematic review by Sylvester 2008

[2] In two studies, patients who recurred at 3 mo prior to starting their additional instillations were already counted as having their first recurrence, potentially diluting the treatment effect size.

Table 59. GRADE evidence profile: One immediate instillation followed by short-term versus long-term instillations during 12 months

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-term	Long-term	Relative (95% CI)	Absolute	
Recurrence											
3[1]	randomised trials	none	none	none	serious[2]	none	156/443 (35.2%)	131/412 (31.8%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Progression (follow-up median 48 months)											
1[3]	randomised trials	none	none	none	serious[2,4]	none	3/210 (1.4%)	7/185 (3.8%)	RR 0.38 (0.1 to 1.44)	23 fewer per 1000 (from 34 fewer to 17 more)	⊕⊕⊕O MODERATE
Treatment-related morbidity											
1[3]	randomised trials	none	none	none	serious[5]	none	NR	NR	-	-	⊕⊕⊕O MODERATE
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester 2008 plus randomised trial in Serretta 2010

[2] Low number of events

[3] Serretta 2010

[4] Confidence interval includes null value

[5] Number of adverse events in each arm not reported. Authors state no significant differences in toxicity between groups

Table 60. GRADE evidence profile: One immediate instillation chemotherapy versus delayed instillations to month 12

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	One immediate dose	Delayed instillations	Relative (95% CI)	Absolute	
Recurrence											
3[1]	randomised trials	none	none	none	serious[2]	none	73/242 (30.2%)	67/270 (24.8%)	RR 1.24 (0.93 to 1.66)	60 more per 1000 (from 17 fewer to 164 more)	⊕⊕⊕O MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester 2008

[2] Small number of events / confidence interval includes null value

Table 61. GRADE evidence profile: One immediate instillation chemotherapy + additional instillations during 6 mo versus delayed instillations during 6 mo

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose + 6mo instillations**	**Delayed instillations 6mo**	**Relative (95% CI)**	**Absolute**	
Recurrence											
2[1]	randomised trials	serious[2]	none	none	none	none	179/398 (45%)	117/239 (49%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester 2008

[2] Immediate instillation not given on same day as TUR in Hendricksen 2007

Table 62. GRADE evidence profile: One immediate instillation chemotherapy + additional instillations during 12 mo versus delayed instillations during 12 mo

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose+12mo instillations**	**Delayed instillations 12 mo**	**Relative (95% CI)**	**Absolute**	
Recurrence											
3[1]	randomised trials	none	none	none	serious[2]	none	128/382 (33.5%)	138/402 (34.3%)	RR 0.97 (0.80 to 1.17)	10 fewer per 1000 (from 69 fewer to 58 more)	⊕⊕⊕O MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester 2008

[2] Small number of events / confidence interval includes null value

Table 63. GRADE evidence profile: Short-term delayed instillations versus long-term delayed instillations

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delayed short-term	Delayed long-term	Relative (95% CI)	Absolute	
Recurrence											
10[1]	randomised trials	none	serious[2]	none	none	none	-	-	not pooled		⊕⊕⊕O MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester 2008

[2] Contradictory results. Range of effects across studies.

Table 64. GRADE evidence profile: Less intense or frequent schedule of chemotherapy versus more intense or frequent schedule of chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Less intense or frequent schedule	More intense or frequent schedule	Relative (95% CI)	Absolute	
Recurrence											
9[1]	randomised trials	none	serious[2]	none	none	none	-	-	not pooled		⊕⊕⊕O MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester 2008

[2] Range of doses and durations of schedules used across studies

Table 65. GRADE evidence profile: Intravesical chemotherapy + BCG versus maintenance BCG alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination therapy	BCG alone	Relative (95% CI)	Absolute	
Recurrence											
5[1]	randomised trials	none	serious[2]	none	serious[3]	none	196/460 (42.6%)	204/437 (46.7%)	RR 0.92 (0.8 to 1.06)	37 fewer per 1000 (from 93 fewer to 28 more)	⊕⊕OO LOW
Recurrence - CIS											
2[1]	randomised trials	none	none	none	serious[3,4]	none	110/207 (53.1%)	91/193 (47.2%)	RR 1.13 (0.93 to 1.37)	61 more per 1000 (from 33 fewer to 174 more)	⊕⊕⊕O MODERATE
Recurrence - Ta/T1											
3[1]	randomised trials	none	none	none	serious[3,4]	none	86/253 (34%)	113/244 (46.3%)	RR 0.75 (0.61 to 0.92)	116 fewer per 1000 (from 37 fewer to 181 fewer)	⊕⊕⊕O MODERATE
Progression											
5[1]	randomised trials	none	serious[2]	none	serious[3,4]	none	51/460 (11.1%)	57/437 (13%)	RR 0.84 (0.59 to 1.2)	21 fewer per 1000 (from 53 fewer to 26 more)	⊕⊕OO LOW
Progression - CIS											
2[1]	randomised trials	none	serious[2]	none	serious[3,4]	none	36/207 (17.4%)	25/193 (13%)	RR 1.33 (0.83 to 2.13)	43 more per 1000 (from 22 fewer to 146 more)	⊕⊕OO LOW
Progression - Ta/T1											
3[1]	randomised trials	none	none	none	serious[4]	none	15/253 (5.9%)	32/244 (13.1%)	RR 0.45 (0.25 to 0.81)	72 fewer per 1000 (from 25 fewer to 98 fewer)	⊕⊕⊕O MODERATE
Overall survival											
0	No evidence										
Disease-specific survival											
0	No evidence										
Treatment-related morbidity											
3[1]	randomised trials	serious[2]	none	none	Serious[5]	none	-	-	-	-	⊕⊕OO LOW
Treatment-related mortality											
0	No evidence										
Health-related quality of life											
0	No evidence										

[1] From meta-analysis in Houghton (2012) plus randomised trial reported in Oosterlinck (2011); [2] Significant statistical heterogeneity; [3] Confidence interval includes null value; [4] Small number of events; [5] Number of events in each arm not reported in Houghton 2012 and Oosterlinck 2011. No difference in toxicity rate between combination therapy and BCG alone.

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Reason: Not randomised trial/outcomes not relevant to PICO

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Reason: Abstract only, insufficient data to be included

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Reason: Comparison not relevant to PICO

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Reason: Superseded by IPD meta-analysis by Malmstrom 2009

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Reason: Duplicate of Serretta 2010

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Reason: Comment on Bohle 2003

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Reason: Relevant to another topic

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Reason: Not randomised trial

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Reason: Excluded from systematic review Shang 2011 (interferon alpha2b not in PICO)

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Reason: Not randomised trial

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Reason: Not systematic review of randomised trials

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Reason: Not a randomised trial

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Reason: Health economics

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Reason: Health economics

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Reason: Expert review

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Reason: Expert review

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Reason: Not relevant to PICO

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Reason: Comment on Malmstrom 2009

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Reason: Retrospective study

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Reason: Non comparative study

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Reason: Relevant to another topic

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Reason: Retrospective study

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Reason: Expert review

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Reason: Non-randomised trial

Zarogianni, C and Tsiamis, C. Immunological treatment of superficial bladder carcinoma. Journal of B.U.On. 2004; 9(1): 41-46.

Reason: Includes non intravesical therapy

Moutzouris, G et al. Prospective, randomized, comparative study of high dose intravesical epirubicin versus BCG for prophylaxis in intermediate risk superficial bladder tumors. European Urology Supplements 2007; 6(2): 171-171.

Reason: Abstract only, Not included in systematic review by Shang 2011

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Reason: Same study as Sylvester 2010

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Reason: Same study as Colombo (2012)

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Reason: Not relevant to PICO (neoadjuvant therapy)

Witjes, JA et al. Clinical Practice Recommendations for the Prevention and Management of Intravesical Therapy-Associated Adverse Events. European Urology Supplements 2008; 7(10): 667-674.

Reason: Expert review

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Reason: Non randomised trial (case series)

Witjes, JA. Management of the first recurrence of T1G3 bladder cancer: Does intravesical chemotherapy deserve a chance? Urologic Oncology-Seminars and Original Investigations 2009; 27(3): 322-324.

Reason: Expert review

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Reason: Comparison not relevant to PICO

Lerner, SP et al. Patterns of recurrence and outcomes following induction bacillus Calmette-Guerin for high risk Ta, T1 bladder cancer. Journal of Urology 2007; 177(5): 1727-1731.

Reason: Comparison not relevant to PICO

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Reason: Abstract only: Cochrane review in progress

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Reason: Not included in Abern 2013

Jeong, CW et al. Comparison of 30 mg and 40 mg of mitomycin C intravesical instillation in Korean superficial bladder cancer patients: prospective, randomized study. Cancer Research & Treatment 2005; 37(1): 44-47.

Reason: Not included in Sylvester 2008

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Reason: Abstract only, not included in Abern 2013

Ayres, BE, Crew, JP, and Action for Bladder Cancer. Is immediate postoperative intravesical chemotherapy beneficial in non-muscle- invasive bladder cancer?. [Review] [33 refs]. BJU International 2010; 105 Suppl 2: 14-17.

Reason: Expert review

Holmang, S. Early Single-Instillation Chemotherapy Has No Real Benefit and Should Be Abandoned in Non-Muscle-Invasive Bladder Cancer. European Urology Supplements 2009; 8(5): 458-463.

Reason: Expert review

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Reason: Not randomised trial

Bartoletti, R et al. Is early single-dose instillation of epirubicin able to improve BCG efficacy in non-muscle invasive high-risk bladder cancer patients? Results from a prospective, randomised, double-blind and controlled study. European Urology Supplements 2008; 7(3): 177-177.

Reason: Same study as Cai 2008

Gulpinar, O et al. The value of perioperative mitomycin C instillation in improving subsequent bacillus calmette-guerin instillation efficacy in intermediate and high-risk patients with non-muscle invasive bladder cancer: a prospective randomized study. International Braz J Urol 2012; 38(4): 474-479.

Reason: Not included in Houghton 2012 (no maintenance BCG)

Lammers, RJ et al. The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive bladder cancer: a systematic review. [Review]. European Urology 2011; 60(1): 81-93.

Reason: Not relevant to PICO (hyperthermia)

Damiano, R et al. Short-term administration of prulifloxacin in patients with nonmuscle-invasive bladder cancer: an effective option for the prevention of bacillus Calmette-Guerin-induced toxicity? BJU International 2009; 104(5): 633-639.

Reason: Comparison not relevant to PICO (toxicity covered in another topic)

Hinotsu, S et al. Sustained prophylactic effect of intravesical bacille Calmette-Guerin for superficial bladder cancer: a smoothed hazard analysis in a randomized prospective study. Urology 2006; 67(3): 545-549.

Reason: Number of events not reported, insufficient data to add to existing meta-analyses

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Reason: Not relevant to PICO

Weiss, C et al. Treatment options for high-risk T1 bladder cancer: status quo and future perspectives of radiochemotherapy. [Review] [67 refs]. Strahlentherapie und Onkologie 2008; 184(9): 443-449.

Reason: Expert review

Gontero, P et al. The impact of intravesical gemcitabine and 1/3 dose Bacillus Calmette-Guerin instillation therapy on the quality of life in patients with nonmuscle invasive bladder cancer: results of a prospective, randomized, phase II trial. Journal of Urology 2013; 190(3): 857-862.

Reason: Possibly relevant to Cochrane review update (Jones et al)

Zhu, S et al. Optimal schedule of bacillus calmette-guerin for non-muscle-invasive bladder cancer: a meta-analysis of comparative studies. BMC Cancer 2013; 13: 332

Reason: No further studies presented/includes non-RCTs)

Sengiku, A et al. A prospective comparative study of intravesical bacillus Calmette-Guerin therapy with the Tokyo or Connaught strain for nonmuscle invasive bladder cancer. Journal of Urology 2013; 190(1): 50-54.

Reason: Comparison not relevant to PICO

Perlis, N et al. Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality-of-evidence review. [Review]. European Urology 2013; 64(3): 421-430.

Reason: Same studies as meta-analysis by Abern (2013)

Inamoto, T. Comparable effect with minimal morbidity of low-dose Tokyo 172 strain compared with regular dose Connaught strain as an intravesical bacillus Calmette-Guerin prophylaxis in nonmuscle invasive bladder cancer: Results of a randomized prospective comparison. Urology Annals 2013; 5(1): 7-12.

Reason: Comparison not relevant to PICO

Ehdaie, B, Sylvester, R, and Herr, HW. Maintenance bacillus Calmette-Guerin treatment of non-muscle-invasive bladder cancer: a critical evaluation of the evidence. [Review]. European Urology 2013; 64(4): 579-585.

Reason: Expert review

Evidence tables

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
Shelley 2000	Systematic review of RCTs published prior to 1999	585 patients from 6 RCTs at medium or high risk of recurrence	<table><tr><td></td><td>TUR (n=281)</td><td>TUR+BCG (n=304)</td></tr><tr><td>Mean age</td><td>65</td><td>64</td></tr><tr><td>Male:female</td><td>3:9</td><td>3:4</td></tr><tr><td>Ta (mean %)</td><td>49%</td><td>41%</td></tr><tr><td>T1 (mean %)</td><td>51%</td><td>59%</td></tr></table> Medium risk – solitary tumour at presentation and tumour recurrence at 3 months or multiple tumours at presentation and no tumours at 3 months. High risk – multiple tumours at presentation and recurrence at 3 months.	TUR + BCG	TUR alone	Maximum f/up for 6 studies ranged from 14-36 months	**Recurrence at 12mo -** lower in BCG treated patients (OR 0.30, 95% CI 0.18 to 0.49) **Toxicities** Cystitis 67%; Fever 25%; Frequency 71%; Haematuria 23%; **Treatment-related mortality** None	Krege 1996; Lamm 1985; Pagano 1990; Pinsky 1985; Melekos 1990; Yamamoto 1990
Sylvester 2002	Systematic review of RCTs published prior to 2002	4,683 patients from 24 trials	<table><tr><td></td><td>N (%)</td></tr><tr><td>No BCG</td><td>2205 (45.3)</td></tr><tr><td>BCG</td><td>2658 (54.7)</td></tr><tr><td></td><td></td></tr><tr><td colspan="2">Disease type</td></tr><tr><td>Papillary</td><td>3967 (81.6)</td></tr><tr><td>Papillary or CIS</td><td>896 (18.4)</td></tr><tr><td></td><td></td></tr><tr><td colspan="2">T category (n=1622)</td></tr><tr><td>Ta</td><td>682 (49.9)</td></tr><tr><td>T1</td><td>684 (50.1)</td></tr><tr><td>Tx</td><td>256</td></tr><tr><td>G1</td><td>533 (37.5)</td></tr><tr><td>G2</td><td>779 (54.9)</td></tr><tr><td>G3</td><td>108 (7.6)</td></tr><tr><td>Gx</td><td>202</td></tr><tr><td></td><td></td></tr><tr><td colspan="2">Treatment comparison (n studies)</td></tr><tr><td>BCG vs. TUR only (2)</td><td>219 (4.5)</td></tr></table>	TUR + BCG	TUR alone or TUR + another treatment	Median 2.5 years, maximum 15 years	**Progression** 9.8% with BCG versus 13.8% control (OR 0.73, 95% CI 0.60-0.89) No reduction in progression noted in 4 trials where BCG maintenance was not used. No significant difference in the treatment effect size across the different control groups used or between the 6 trials comparing MMC to BCG. **Survival, death from any cause** 23.2% BCG vs. 26.7% control (OR 0.89, 95% CI 0.75 to 1.06)	Cookson 1997; Pagano 1991; Badalament 1987; Lamm 2000; Palou 2001; Rintala 1996; Rintala 1995; Witjes 1998; Lamm 1995; Malmstrom 1999; Nogueira 2001; Rintala 1991; Vegt 1995; Witjes 1998; de Reijke 2001; ven der Meijden 2001; Brosman 1982; Martinez-Pineiro 1990; Witjes 1999; Jimenez-Cruz 1997; Kalbe 1994; Kalbe

Study, country	Study type, study period	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			BCG maint vs. No maint (3)	603 (12.4)				**Disease-specific survival, death from bladder cancer** 5.6% BCG vs. 7.7% control (OR 0.81, 95% CI 0.58 to 1.13)	1991; Melekos 1993; Ibrahiem 1988; Lamm 1991; Herr 1995.
			BCG+MMC vs. MMC (3)	432 (8.9)					
			BCG vs. MMC (6)	1891 (38.9)					
			BCG vs. epirubicin (2)	1005 (20.7)					
			BCG vs. TUR only or epirubicin (1)	161 (3.3)					
			BCG vs. thiotepa (1)	49 (1.0)					
			BCG vs. Doxorubicin or thiotepa (1)	176 (3.6)					
			BCG vs. Interferon α (2)	189 (3.9)					
			BCG vs. Bropirimine (1)	53 (1.1)					
			BCG vs. Keyhole limpet hemocyanin (1)	38 (0.8)					
			BCG vs. TUR only or maltose tetrapalmite (1)	47 (1.0)					
			BCG maintenance						
			No maintenance (4)	593 (22.3)					
			Maintenance (10)	2065 (77.7)					
			BCG strain						
			Tice (6)	1034 (38.9)					
			Connaught (6)	641 (24.1)					
			Pasteur (9)	603 (22.7)					
			RIVM (2)	320 (12.0)					
			Frappier (2)	60 (2.3)					
Han 2006	Systematic review of RCTs or controlled observational cohort studies published 1997 to 2005	4767 patients from 24 trials		N (%)	BCG+TUR	TUR alone or TUR + another treatment	Not reported	**Recurrence** 40.5% BCG versus 49.7% no BCG (OR 0.61, 95% CI 0.46 to 0.80) Papillary tumours (OR 0.50, 95% CI 0.33 to 0.75) CIS (OR 0.90, 95% CI 0.63 to 1.28) Papillary and/or CIS (OR 0.19, 95% CI 0.02 to 1.56) T1G3 (OR 0.55, 95% CI 0.21 to 1.42)	Altay 2000; Ayed 1998; Chepurov 2002; Hara 2003; Irie 2003; Jimenez-Cruz 1997; Kassine 2002; Kassinen 2003; Kolodziej 2002; Lamm 2000; Librenjak 2003; Malmstrom 1999; Martinez-Pineiro 2002; Moyano Calvo 1999; Patard 2002;
			No BCG	2425 (49.7)					
			BCG	2342 (40.5)					
			Treatment comparison (n studies)						
			BCG vs. TUR only (9)	1100 (23.1)					
			BCG vs. BCG + chemo/immunotherapy	764 (16)					
			BCG vs. immunotherapy	1110 (23.3)					
			BCG vs. chemotherapy	1793 (37.6)					
			BCG maintenance						
			No maintenance (8)	2072 (65.9)					

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			Maintenance (10) 1070 (34.1) BCG strain Connaught 1350 (40.1) Tokyo 172 178 (5.3) Pasteur 496 (14.7) Other (Tice, RIVM) 1342 (39.9)				**Toxicity** Cystitis, dysuria, frequency/urgency, fever, malaise, chills, nausea were significantly more frequent in the BCG group than chemo/immunotherapy group. 30% MMC developed local toxicity versus 44% BCG.	Peyromaure 2004; jke 2005; Sekine 2001; Shakin 2003; Tong 2003; Tozawak 2001; van der Meijden 2001; Witjes (EORTC) 1998; Witjes 1998; Yumura 2004
Pan 2008	Meta-analysis of RCTs or controlled observational cohort studies published 2000 to 2005	1648 T1G3 patients from 13 trials	N (%) Treatment comparison (n studies) BCG vs. TUR only (9) 1064 (64.6) BCG vs. Chemotherapy (1) 67 (4.1) BCG maintenance vs. No BCG maint (1) 126 (7.6) BCG (T1G3) vs. BCG (other grades) (3) 203 (12.3) BCG standard dose vs. BCG low dose (1) 188 (11.4) BCG strain Connaught 614 (37.3) Polish or Tice 155 (9.4) Pasteur 692 (42) Dannish 1331 90 (5.5)	TUR+BCG	TUR alone or TUR + other treatment	Not reported	**Recurrence** 41% BCG versus 45.3% no BCG (OR 0.58, 95% CI 0.41 to 0.83) **Toxicity** Cystitis, dysuria, frequency/urgency, fever, malaise, chills, nausea were significantly more frequent in the BCG group than chemo/immunotherapy group.	
Huncharek 2000	Meta-analysis of RCTs published 1966 to 1997	3703 patients from 11 trials	Ta or T1 primary tumours. No patients with CIS. Five studies included G1, G2 tumours only and 7 studies also included G3 tumours. Adriamycin was the most commonly used drug (8 treatment arms) followed by Mitomycin (7 arms).	TUR + adjuvant intravesical chemotherapy	TUR alone	Minimum 1 year	**Recurrence at 1 year** OR 0.56 (95% CI 0.48 to 0.65) for intravesical chemotherapy reducing recurrence at 1 year. However significant heterogeneity across studies (Q=55.6). Sub-analysis indicated improved effect with longer treatment schedules.	Hirao 1992; 1994; Akaza 1987; Niijima 1983; MRC 1994; Tolley 1996; Togashi 1992; Hirao 1987; Krege 1996; Flamm 1995; Tsushima 1987

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
							Short-term treatment (single instillation or up to 2 months) 1258 patients OR 0.70 (0.55 to 0.90) – chemo reduces tumour recurrence at 1 year by 30%. Similar for 2-year recurrence (32% (0.54-0.85) 1-yearmultiple treatment protocols, 1721 patients OR 0.65 (0.46 to 0.80) 2-year treatment protocol, 575 patients OR 0.27 (0.19 to 0.39) – 2 year recurrence. Numbers of events in each group not reported	
Huncharek 2001	Meta-analysis of RCTs published 1966 to 1997	1609 patients from 8 RCTs	Ta or T1 recurrent cancer. 3 trials included CIS. Adriamycin was the most commonly used drug (6 treatment arms) followed by thiotepa, epirubicin and mitomycin which were used as single agents in two arms (6 arms total).	TUR + adjuvant intravesical chemotherapy	TUR alone	Minimum 1 year	**Recurrence at 1 year** OR 0.62 (95% CI 0.51 to 0.76) for intravesical chemotherapy reducing recurrence at 1 year by 38%. No evidence of heterogeneity. **Recurrence at 2 years** OR 0.46 (0.33 to 0.63) **Recurrence at 3 years** OR 0.35 (0.23 to 0.54) Statistical heterogeneity at 2 and 3 years not explained by differences in treatment duration. Drug type was a major contributor to heterogeneity. Adriamycin OR 0.57 (0.43 to 0.75). Other drugs OR 0.27 (0.19 to 0.37). Therefore adriamycin less effective than other drugs.	Ali-el-dein 1997; Gustafson 1991; Kim 1989; Kurth 1997; Obata 1994; Prout 1983; Rubben 1988; Schulman 1982
Huncharek 2004	Meta-analysis of RCTs published	2427 patients from	Ta or T1 with or without CIS. Minimum of 20 patients per arm and minimum of 2 years	TUR+BCG	TUR + chemotherapy	Minimum 2 years	**Progression** OR 1.24 (0.95 to 1.61) favouring BCG but CI includes null effect	Lamm 1995; Malmstrom 1999; Martinez 1990;

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
	1966 to 2002	8 RCTs	follow-up. Mitomycin was the most commonly used drug (4 trials) All but 2 trials included patients previously treated with intravesical chemotherapy.				suggesting uncertainty. No heterogeneity. Subgroup analyses of MMC vs. BCG (4 trials 1478 patients) OR 1.04 (0.76 to 1.42) suggesting no difference in risk of progression. MMC maybe most effective agent. Pooled OR of 2 trials (781 patients) excluding patients previously treated with chemo = 0.75 (0.45 to 1.25) in favour of MMC. Pooled OR of trials only including patients previously treated with chemo = 1.49 (1.09 to 2.03) in favour of BCG. Number of total events in each arm not reported	Melekos 1996; Melekos 1996b; Vegt 1995; Witjes 1998; van der Meijden 2001
Huncharek 2003	Meta-analysis of RCTs published 1990 to 1999	2261 patients from 9 randomised trials	Ta or T1 with or without CIS, no prior radiation to the bladder. 5 trials used MMC in chemo arm, 2 used epirubicin All but 2 trials included patients previously treated with intravesical chemotherapy.	TUR+BCG	TUR+ chemotherapy	Minimum 2 years	**Recurrence** 1-year. OR 0.89 (95% CI 0.74 to 1.07), sign heterogeneity Studies including prior chemotherapy OR 0.54 (0.43 to 0.69) in favour of BCG Studies excluding prior chemo OR 1.82 (1.37 to 2.41) in favour of MMC No heterogeneity in subgroup analyses. Similar results for 2-year and 3-year recurrence rates in subgroup analyses.	Lamm 1991; Lamm 1995; Martinez 1990; Malmstrom 1999; Melekos 1996; Melekos 1996b; Rintala 1991; Vegt 1995; Witjes 1998
Sylvester 2005	Meta-analysis of RCTs published 1990 to 2003	700 patients from 9 RCTs	<table><tr><td></td><td>N (%)</td></tr><tr><td>BCG</td><td>345 (39.3)</td></tr><tr><td>Chemotherapy</td><td>355 (50.7)</td></tr><tr><td></td><td></td></tr><tr><td>CIS</td><td>594 (84.9)</td></tr><tr><td>Dysplasia</td><td>106 (15.1)</td></tr></table>	TUR+BCG	TUR+ chemotherapy	Median 3.6 years, maximum 11.9 years	**Complete response (-ve cytology, cystoscopy and biopsy)** 68.1% on BCG vs. 51.5% chemotherapy (OR 0.53, 0.38 to 0.74).	Lamm 1995; Vegt 1995; Di Stasi 2003; Lamm 1991; de Reijke 2004; Sekine 2001; Witjes 1998; Malmstrom 1999;

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			<table><tr><td></td><td></td></tr><tr><td colspan="2">Concomitant papillary tumours</td></tr><tr><td>No</td><td>256 (36.6)</td></tr><tr><td>Yes</td><td>444 (63.4)</td></tr><tr><td></td><td></td></tr><tr><td colspan="2">Treatment comparison</td></tr><tr><td>BCG vs. MMC</td><td>347 (49.6)</td></tr><tr><td>BCG vs. adriamycin</td><td>143 (20.4)</td></tr><tr><td>BCG vs. epirubicin</td><td>168 (24)</td></tr><tr><td>BCG vs. MMC/adriamycin</td><td>42 (6)</td></tr><tr><td></td><td></td></tr><tr><td colspan="2">BCG maintenance</td></tr><tr><td>No maintenance (8)</td><td>21 (5.9)</td></tr><tr><td>Maintenance (10)</td><td>334 (94.1)</td></tr><tr><td></td><td></td></tr><tr><td colspan="2">BCG strain</td></tr><tr><td>Connaught</td><td>148 (42.9)</td></tr><tr><td>Tokyo 172</td><td>21 (6.1)</td></tr><tr><td>Pasteur</td><td>83 (24.1)</td></tr><tr><td>TICE</td><td>54 (15.7)</td></tr><tr><td>RIVM</td><td>39 (11.3)</td></tr></table>				**Recurrence in complete responders** 34% BCG vs. 50% chemo recurred during f/up. OR =0.47 (0.31 to 0.73) **Disease-free** 46.7% BCG vs. 26.2% chemo OR treatment failure 0.41 (0.30 to 0.56) in favour of BCG. BCG only superior to MMC when maintenance was given (OR 0.57, 0.34 to 0.97) **Progression** 15.4% BCG vs. 19.6% chemo (OR 0.74, 0.45 to 1.22) **Survival** 2 studies. 13.3% (14/105) chemo vs. 10.5% (11/105) BCG died due to bladder cancer. 35.9% (80/223) chemo vs. 34.2% (63/184) BCG died from any cause.	Martinez-Pineiro 1990
Bohle 2003	Meta-analysis of RCTs or retrospective cohort studies published 1985 to 2000	2749 from 9 prospective trials and 2 observational studies	Mostly intermediate and high risk groups included in the trials. Low risk tumours not documented in included studies	BCG	MMC	Median 26mo range 11.5 to 50.4	**Recurrence** 38.6% BCG vs. 46.4% MMC (RR 0.75, 95% CI 0.61 to 0.94) In BCG maintenance subgroup RR 0.64 (0.52 to 0.79) in favour of BCG. In no BCG maintenance subgroup RR 0.95 (0.72 to 1.25) **Toxicity** 5 studies (901 BCG patients and 776 MMC patients). 2 studies reported details on all relevant adverse reactions. Cystitis 53.8% BCG vs. 39.2%	DeBruyne 1992; Krege 1996; Vegt 1995; Lamm 1995; Lundholm 1996; Nogueira 2000; Pagano 1987; Lee 1992; Juahiainen 1989; Ayed 1998; Milan 2000

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
							MMC (OR 1.81, 1.48 to 2.23). No difference between maintenance and no maintenance BCG. Local and systemic toxicity more frequent in BCG group, except for allergy and skin reactions which were more common in MMC group. Slightly more patients were withdrawn from BCG studies than MMC due to adverse reactions.	
Mangiarotti 2008	Randomised trial	92 intermediate risk NMIBC	No previous treatment with chemo or immuno therapy N (92) Mean age 64 yrs M/F 67/25 Ta/T1 53/39 G1/G2 57/35	BCG TICE strain one month after TUR. 6 wk induction plus monthly maintenance over 12 mo	MMC 40mg/50ml once a wk for 8 wks plus 12 monthly maintenance	Mean 65.7 months (12-108)	**Recurrence** 23/46 (50%) MMC versus 23/46 (50%) BCG **Toxicity** Cystitis: 10 MMC, 19 BCG Haematuria: 2 MMC Hypersensitivity: 10 MMC Severe epididymitis: 1 BCG Fever: 2 BCG	Method of randomisation, allocations concealment not reported. Recurrence data added to meta-analyses by Bohle 2003
Bohle 2004	Meta-analysis of RCTs or retrospective cohort studies published 1985 to 2000	2410 patients from 7 clinical trials and 2 retrospective comparative cohort studies	No information provided	BCG	MMC	Median 26mo range 11.5 to 50.4	**Progression** Overall 98/1127 (7.7%) BCG vs. 107/1133 (9.4%) MMC. RR 0.79 (0.61 to 1.03) No difference by BCG strain, BCG dose, MMC dose, number of MMC instillations, follow-up duration	DeBruyne 1992; Krege 1996; Vegt 1995; Lamm 1995; Nogueira 2000; Juahiainen 1989; Ayed 1998; Milan 2000; Malmstrom 1999
Malmstrom 2009	IPD meta-analysis of randomised trials published	2820 patients from 9 randomised trials	MMC N (%) / BCG N (%) Prior intravesical chemotherapy No: 1117 (93.6) / 1196 (92.9)	BCG	MMC	Median 4.4 years, Maximum 17.7 years	**Recurrence** Overall no difference between BCG and MMC. In trials with BCG maintenance 32% reduction in the risk of	Krege 1996; Lamm 1995; Malmstrom 1999; Witjes 1998; Ojea 2007; Friedrich 2007; Di Stasi 2003;

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
	1991-2007		Yes: 76 (6.4) / 91 (7.1) Tumour status Primary: 828 (71.5) / 849 (70) Recurrent: 330 (28.5) / 363 (30) Tumour status Solitary: 598 (53.3) / 571 (48.9) Multifocal: 524 (46.7) / 597 (51.1) Stage Ta: 726 (55.3) / 708 (51.7) T1: 538 (41) / 601 (43.9) CIS: 37 (2.8) / 48 (3.5) Dysplasia: 11 (0.8) / 12 (0.8) Grade G0: 4 (0.3) / 3 (0.2) G1: 332 (25.2) / 339 (25) G2: 766 (58.1) / 794 (58.5) G3: 217 (16.5) / 221 (16.3) CIS No: 1181 (87) / 1255 (88.4) Yes: 177 (13) / 164 (11.6) Risk group Low: 44 (3.3) / 48 (3.5) Intermediate: 964 (73.3) / 1019 (74.7) High: 307 (23.3) / 297 (21.8) BCG maintenance No: 770 (55.7) / 726 (50.5) Yes: 613 (44.3) / 711 (49.5)				recurrence for BCG compared to MMC. 28% increase in the risk of recurrence for BCG in trials without BCG maintenance. BCG maintenance was more effective than MMC in both patients previously treated with chemo and those not. **Progression, overall survival, disease specific survival** (7 studies, 1880 patients) 12% progressed to MIBC, 24% died and of those 30% died due to bladder cancer – no significant differences between MMC and BCG for these end-points.	Rintala 1991; Witjes 1996
Sylvester 2004	Meta-analysis of randomised trials published before Jan 2003	1476 patients from 7 trials	TUR alone N (%) / TUR+chemo N (%) Intravesical chemotherapy Epirubicin: 340 / 334 (44.7) MMC: 22 / 206 (27.6) Thiotepa: 130 / 126 (16.9) Pirarubicin: 79 / 81 (10.8) Tumour status Primary: 683 (89.3) / 660 (89.1)	TUR + one intravesical instillation of chemotherapy	TUR alone	Median 3.4 years, (range 2 to 10.7), maximum 14.5 yrs	**Recurrence** 362 (48.4%) TUR alone versus 267 (36.7%) chemo (OR 0.61, 95% CI 0.49 to 0.75) No benefit in the trial using thiotepa. Single tumours OR 0.61 (0.46 to 0.80). Multiple tumours OR 0.44 (0.18 to 1.02).	Oosterlink 1993; Ali-el-Dein 1997; Rajala 2002; Tolley 2003; Solsona 1999; MRC 1985; Okamura 2002

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			Recurrent: 82 (10.7) / 81 (10.9) Tumour status Solitary: 639 (83.5) / 630 (85) Multifocal: 126 (16.5) / 111 (15) Stage Ta: 525 (69.8) / 479 (65.9) T1: 227 (30.2) / 248 (34.1) Grade G1: 381 (50.1) / 326 (44.5) G2: 320 (42.1) / 324 (44.2) G3: 59 (7.8) / 83 (11.3)				**Toxicity** Mild transient, irritative bladder symptoms including dysuria, frequency, and macroscopic heamaturia, most frequent occurring in 10% of all patients. Systemic toxicity was rare. Allergic skin reactions 1 to 3% of patients in two studies (epirubicin and MMC)	
Abern 2013	Meta-analysis of randomised trials	3103 patients from 18 trials published between 1976 to 2011	Dwell time ranged from 25 to 120 minutes, with 60 mins being most commonly reported duration of therapy.	TUR + one intravesical instillation of chemotherapy	TUR alone	Not reported	**Recurrence** 769/1527 (50%) TUR only vs. 577/1576 (37%) TUR+IVC group. RR 0.67 (0.56-0.79). NNT 7.2 patients to avoid 1 recurrence. Gem and interferon a-2b did not show a benefit on recurrence. Tumour risk factors (stage, grade, multiple, recurrent) did not alter the efficacy of single dose chemo. No clear dose-response relationship. To examine heterogeneity De Nunzio study was excluded which increased RR from 0.67 to 0.71 (0.62-0.82) and reduced heterogeneity from 75% to 61%.	Funnel plots suggest existence of publication bias- small trials disproportionally contribute to the protective effect of chemo
Turkeri 2010 Turkey	Randomised trial 2002-2004	299 randomised, 143 analysed	Primary and solitary or multiple (3 or less) tumours. Excluded CIS, incomplete TUR, over 80 yrs old, WHO PS >2 Age: Single dose N (%) 59 / Double dose N (%) 62	Single dose 100mg epirubicin within 6 hours plus 100mg 12-18 hours after TUR	Single dose 100mg epirubicin within 6 hours	16.9 months	**Recurrence** 10/68 (14.7%) single dose versus 16/75 (21.3%) double dose, non-significant. No difference in probability of recurrence-free survival. **Progression** 2/68 (2.9%) single dose versus	Withdrawals not accounted for – no intent-to-treat analysis. Method of randomisation not specified.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			Male: 61 (88); 66 (88) Female: 7 (12); 9 (12) Ta: 37 (54); 39 (52) T1: 31 (46); 36 (48) Grade G1: 13 (19); 13(17) G2: 53 (78); 60 (80) G3: 2 (3); 2 (3)				6/75 (8%) double dose (RR 0.37, 0.08 to 1.76)	
Saika 2010 Japan 1995-2001	Randomised trial	303 enrolled, 257 eligible	Primary or recurrent NMIBC. Excluded CIS, previous MIBC, incomplete TUR	Group A: 2x20mg/40ml epirubicin less than 1 hr after TUR and in early morning of next day, OR Group B: 2x50mg/100ml in same schedule as group A	Group C: TUR only	Median 44 months (1-70)	**Recurrence free survival** 24, 38 and 13 months for Group A, B and C. Only significant difference between Group B and C (longer RFS for B) **Toxicities** Local Grade 1 - 22.9% Group A versus 35.6% Group B (RR 0.63, 0.39 to 1.02). No severe local toxicities.	
Shuin 1994 Japan 1990-1993	Randomised trial	68 randomised, 65 analysed	Recurrent NMIBC Grade 1-2. ADR N (%); EPI N (%) Male: 27 (82); 26 (81) Female: 6 (18); 6 (19) Previous treatment No: 12 (36); 10 (31) Yes: 21 (64); 22 (69)	30mg/40ml adriamycin for 2h. Every 2 wks for first 3 mo after TUR then every 4 wks for 1yr	30mg/40ml epirubicin for 2h. Every 2 wks for first 3 mo after TUR then every 4 wks for 1yr	Not reported	**Recurrence** 9/33 (27%) adriamyicn versus 8/32 (25%) epirubicin Tumour-free period 8.5 mo versus 9.7 mo epirubicin **Toxicity** Adriamycin – 2 (6%) pollakisuria, 2 (6%) pain on urination, 2 (6%) haematuria Epirubicin – 5 (15%) pollakisuria, 5 (15%) pain on urination, 4 (12%) haematuria. No systemic side-effects	Method of randomisation and length of follow-up not reported.
Eto 1994 Japan 1990-1992	Randomised trial	150 enrolled, 114 evaluable	Ta, T1 bladder cancer, Exclude CIS, previous treatment with doxorubicin, EPI N (%); ADR N (%) Mean age: 68.8; 61.9	30mg/30ml adriamycin twice a week for 4 wks then monthly for 11 months (19	30mg/30ml epirubicin twice a week for 4 wks then monthly for 11	Mean 674 days EPI, 606 days adriamycin	**Recurrence** 2 year – 7/60 (11.6%) epirubicin versus 10/54 (18.5%) doxorubicin **Toxicity**	

Study, country	Study type, study period	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			Male	51 (85)	47 (87)	instillations)	months (19 instillations)		Local toxicity – 18/60 epirubicin versus 16/54 adriamycin	
			Female	9 (15)	7 (13)					
			History							
			Primary	46 (76)	41 (76)					
			Recurrent	8 (13)	8 (15)					
			Tumour size							
			<1	27 (45)	27 (50)					
			1-3	24 (40)	25 (46)					
			3-5	8 (13)	2 (4)					
			>5	1 (2)	0					
			N tumours							
			Solitary	28 (47)	34 (63)					
			2-4	23 (38)	12 (22)					
			Stage							
			Ta	21 (35)	17 (31)					
			T1	29 (48)	31 (57)					
			Grade							
			G1	20 (33)	11 (20)					
			G2	29 (48)	36 (67)					
			G3	7 (12)	4 (7)					
Sylvester 2008	Systematic review of randomised trials comparing the schedule and duration of intravesical chemotherapy published before 2007	23 randomised trials included.	Varied across studies			Intravesical chemotherapy instillations	Number, frequency, timing, duration, dose of instillations	Varied across studies	One immediate instillation after TUR reduces the recurrence rate and is recommended in all patients with papillary tumors except in the case of a perforated bladder or extended TUR (grade A). In patients at low risk of recurrence, no further treatment is recommended prior to recurrence. In patients with multiple tumors for whom one instillation is insufficient treatment, the results of this systematic review are inconclusive and firm recommendations cannot be provided. The effect of one	MRC 1985, 1994; Tolley 1988, 1996; Selvaggi 1990; Bouffioux 1995; Okamura 1998; Koga 2004; Ali-el-Dein 1997; Liu 2006; Hendrickson 2007; Iborra 1992; Ueda 1992; Nomata 2002; Rubben 1988; Kuroda 2004; Flamm 1989, 1990; Huland 1990; Schwaibold 1997; Friedrich 2007; Mitsumori 2004; Au 2001; Akaza 1987; Niijima 1983; Ali-el-

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
							immediate instillation lasts for approximately 1.5 yr (level of evidence 1B). Additional instillations may be able to further reduce the recurrence rate although no recommendations can be given concerning their optimal duration. A short intensive schedule of instillations within the first 3–4 mo after an immediate instillation may be as effective as longer term treatment schedules (grade C). Additional instillations at or after 1 yr may be useful in preventing late recurrences in intermediate-risk patients, but results of trials studying the benefit of 1, 2, and 3 yr of treatment are conflicting (grade C). Long-term instillations during ≥1 yr seem advisable only when an immediate instillation has not been given (grade C). Higher drug concentrations and optimization of the drug's concentration in the bladder by decreasing the urine volume and controlling urine pH may provide better results (grade C).	Dein 1997; Koontz 1981.
Serretta 2010	Randomised trial	577 randomised, 395 analysed	Intermediate risk. No chemotherapy in previous 12 mo, no previous BCG	One instillation Epirubicin within 6 h (80mg/50ml)	One instillation Epirubicin within 6 h	Median 48 (3-78) mo	**Recurrence** 63/210 (30%) short term vs. 54/185 (29.2%) long term	No intent-to-treat analysis, 87 patients missing data.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			N (%) Median age 68 (35-97) male 417 (86.5) Female 65 (13.5) Primary 290 (60.2) Recurrent 192 (39.8) Single 256 (36.6) Multiple 444 (63.4) TaG1-G2 174 (36.1) T1G1 108 (22.4) T1G2 200 (41.5)	plus 5 weekly instillations then monthly maintenance for 10 mo (16 instillations)	(80mg/50ml) plus 5 weekly instillations (6 instillations)		(p=0.43) **Recurrence free rate** Only significant in favour of maintenance during 1st 18 months of TUR Benefit of maintenance in patients with primary multiple tumours and G1 tumours. **Progression** 10 patients progressed (3 short-term, 7 long-term) **Toxicity** No differences between arms. During induction 11 (2.2%) fever >38°, 2 (0.4%) allergic skin reaction, 35 (7.1%) treatment interruption during induction due to dysuria and urgency.	Underpowered for subgroup analysis
Shang 2011	Systematic review of randomised trials	1,111 patients from 5 trials published prior to 2010	Intermediate and high risk Ta T1 bladder cancer. Patients with CIS were excluded	TUR+BCG	TUR +epirubicin	Not reported	**Recurrence** 195/549 (35.5%) BCG versus 289/562 (51.4%) EPI (RR 0.69, 95% CI 0.60 to 0.79) **Progression** 8% BCG vs. 10% EPI (RR 0.78, 95% CI 0.54 to 1.13) **Overall mortality** No significant differences RR 0.86, 95% CI 0.71 to 1.04, p=0.12 **Disease-specific mortality** No significant differences RR	Cheng 2005; Melekos 1993; Melekos 1996a; Melekos 1996b; Sylvester 2010

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
							0.94, 95% CI 0.23 to 3.80, p=0.93 **Toxicity** Cystitis 54.1% BCG vs. 31.7% EPI (RR 1.92, 1.38 to 2.65) Heamaturia 30.8% vs. 16.1% (RR 1.90, 1.47 to 2.45) Systemic side-effects 34.8% BCG vs. 1.3% EPI (RR 0.53, 2.25 to 143.91)	
Jones 2012	Systematic review of randomised trials published prior to 2011	704 patients from 6 trials (3 trials comparing BCG with Gemcitabine)	Varied across studies. All superficial bladder cancer.	TUR+BCG	TUR + Gemcitabine	Varied across studies	3 trials comparing BCG and Gem not pooled due to clinical heterogeneity (1 trial of BCG failure – not relevant to this topic). One trial of patients at intermediate risk of recurrence (primary Ta-T1, no CIS) showed that BCG and Gem were similar for recurrence (25% vs. 30%) and progression. Dysuria and frequency were less with Gem. Another trial of high risk patients, recurrence was higher for Gem than BCG (53% vs. 28%) and time to recurrence shorter with Gem (3.9 vs. 3.1 months). On trial of Gem vs. MMC showed lower rates of recurrence with Gem (28% vs. 39%) and progression (11% vs. 18%) but were non-significant. Global incidence of adverse events were significantly less with Gem (38.8% vs. 72.25, p=0.02)	BCG vs. Gem – Bendary 2011; Porena 2010; Lorenzo 2010 (BCG refractory Topic F3) Gem vs. MMC – Addeo 2010 Gem (single instillation) vs. placebo – Bohle 2009 Gem single dose vs. 1 dose/week vs. 2 doses/week – Gardmark 2005

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
Yalcinkaya 1998 Turkey	Prospective trial (unclear whether randomised) 1990-1994	80 NMIBC	<table><tr><td></td><td>Group 1</td><td>Group 2</td></tr><tr><td>Age</td><td>55.3</td><td>56.3</td></tr><tr><td>Female</td><td>3</td><td>4</td></tr><tr><td>Male</td><td>22</td><td>21</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Tumour status</td><td></td><td></td></tr><tr><td>Primary</td><td>19</td><td>17</td></tr><tr><td>Recurrent</td><td>6</td><td>8</td></tr><tr><td>Tumour status</td><td></td><td></td></tr><tr><td>Solitary</td><td>13</td><td>13</td></tr><tr><td>Multifocal</td><td>12</td><td>12</td></tr><tr><td>Stage</td><td></td><td></td></tr><tr><td>Ta</td><td>10</td><td>12</td></tr><tr><td>T1</td><td>15</td><td>13</td></tr><tr><td>Grade</td><td></td><td></td></tr><tr><td>G1</td><td>6</td><td>9</td></tr><tr><td>G2</td><td>14</td><td>13</td></tr><tr><td>G3</td><td>4</td><td>3</td></tr></table>	81mg Connaught BCG weekly for 6-wks	54mg Connaught BCG weekly for 6-wks	Mean 33.5 months	**Recurrence** 9/40 (22.5%) 81mg vs. 16/40 (40%) 54mg **Progression** 1/40 (2.5%) 81mg vs. 2/40 (5%) 54mg **Toxicity** No sig differences in side effects between groups. 60% vs. 47.5% cystitis, 30% vs. 25% flu-like symptoms, 15% vs. 35% haematuria.	No details of randomisation method, blinding or allocation concealment. Reports significant difference in recurrence but no statistics reported
Agrawal 2007 India	Randomised trial 2002-2005	152 with NMIBC. 128 assessed for outcomes	Excluded CIS, previous iv therapy, >2 recurrences Age range 45-84 years. 92 Male, 36 female	Modified Danish strain 1331 BCG 6-weekly induction plus 1yr maintenance	3 groups: 120mg v. 80mg v. 40mg	Mean 36 months	**Recurrence** 8/40 (20%) 40mg, 12/48 (25%) 80mg, 8/40 (20%) 120mg **Progression** No events in any group. **Dysuria** 30% v 33% v 70% **Frequency** 20% v 33% v 60% **Haematuria** 0% v 8% v 30% **Fever >39°C** 0% v 0% v 30%	No details of randomisation method, blinding or allocation concealment. 24 patients excluded from analysis due to low compliance
Ojea (2007)	Randomised trial 1995 to 1998	430 M 87% / F 13% 47% ≤65 yrs, 52% >65yrs	Intermediate risk (TaG2 and T1G1-2) without CIS <table><tr><td></td><td>N (%)</td></tr><tr><td>Primary</td><td>316 (73.5)</td></tr><tr><td>Recurrent</td><td>114 (26.5)</td></tr><tr><td>No. of tumours</td><td></td></tr><tr><td>1</td><td>211 (49.1)</td></tr></table>	27mg (1/3 dose) BCG; 13.5mg (1/6 dose) BCG (Connaught strain); 30mg MMC 14-21 days after TUR, weekly for 6 wks, followed	3-arm trial	53 months (0-111) for MMC group; 57 (0-114) for BCG 27mg group; 61 (0-112) for BCG	**Recurrence** MMC 38.9% vs. BCG 27mg 26.8% vs. BCG 13.5mg 36% Significant difference between BCG 27mg vs. MMC, no difference between BCG 27mg and 13.5mg or MMC and BCG 13.5 mg.	33 did not complete treatment but were included in final analysis

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			2: 59 (13.7) 3: 46 (10.7) >3: 116 (25.6) Tumour size ≤1cm: 115 (26.7) 2cm: 132 (30.7) 3cm: 94 (21.9) >3cm: 89 (20.7) TG category TaG2: 57 (13.3) T1G1: 97 (22.6) T1G2: 276 (64.2)	by every 2 wks over 12 wks		13.5mg group	**Progression** No differences among the 3 groups (MMC 9.4% vs. BCG 27mg 9.9% vs. BCG 13.5mg 12.9%) **Cancer-specific survival** No significant differences (MMC 4.7% vs. BCG 27mg 2.1% vs. BCG 13.5mg 3.6%) **Toxicity** Local toxicity: 65% (n=93) BCG 27mg group; 64% (n=89) BCG 13.5mg group Systemic toxicity: 11% (n=16) BCG 27mg group; 11% (n=15) BCG 13.5mg group. No significant differences between BCG groups. Significantly more toxicity with BCG than MMC.	
Martinez-Pineiro (2005) 1995-1999	Randomised trial 1995 to 1999	155 M 92% / F 8% Mean age 67 (range ns)	T1G3 and Tis bladder tumours N (%) Primary: 108 (69.7) Recurrent: 47 (30.3) No. of tumours 1: 211 (49.1) 2: 59 (13.7) 3: 46 (10.7) >3: 116 (25.6) Tumour size ≤1cm: 73 (47.1) 2cm: 28 (18.1) 3cm: 18 (11.6) >3cm: 36 (23.2) TG category T1G3: 90 (58.1) Tis primary: 23 (14.8)	81mg BCG (standard dose); (Connaught strain) 7-14 days after TUR, weekly for 6 wks, followed by every 2 wks, 6 more times	27mg BCG (reduced dose)	61 months (range 3-102)	**Recurrence** 39% 81mg vs. 45% 27mg, Time to recurrence HR 1.23 (0.75-1.99) p=0.405 **Progression** 24.3% 81mg vs. 26% 27mg, Time to progression HR 1.09 (0.58-2.03) p=0.80 **Cancer-specific death** 12% 81mg vs. 15% 27mg, HR 1.25 (0.53-2.94), p=0.613 **Toxicity** Local toxicity Grade 1-2: 50% (n=41) standard dose; 37% (n=27) reduced dose Grade 3-4: 20% (n=16) standard dose; 11% (n=8) reduced dose	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			TisTaG3: 9 (5.8) TisT1G3: 33 (21.3)				Withdrawn from study: 12% (n=10) standard dose; 10% (n=7) reduced dose. Systemic toxicity 15.9% vs. 5.5%, p=0.043)	
Martinez-Pineiro (2002) 1991-1992	Randomised trial 1991 to 1992	500 M 90% / F 10% Mean age 63 (range ns)	Superficial bladder cancer (TaG2-3/T1G1-3) with or without concomitant CIS or primary CIS. Patients with TaG1 tumours were admitted only if recurrent. N (%) Primary: 308 (61.6) Recurrent: 192 (38.4) No. of tumours 1: 283 (56.6) 2: 82 (16.4) 3: 41 (8.2) >3: 94 (18.8) Tumour size ≤1cm: 163 (32.6) 2cm: 127 (25.4) 3cm: 100 (20) >3cm: 110 (22) TG category Ta: 129 (25.8) T1: 332 (66.4) Tis primary: 13 (2.6) Tis Ta: 5 (1) Tis T1: 21 (4.2) G1: 86 (17.2) G2: 317 (63.4) G3: 97 (19.4)	81mg BCG (standard dose) (Connaught strain) 7-14 days after TUR, weekly for 6 wks, followed by every 2 wks, 6 more times	27mg BCG (reduced dose)	69 months (maximum 109	**Recurrence** 28.1% standard versus 30.7% reduced dose. Time to first recurrence HR 1.09 (0.79-1.51) **Progression** 11.5% standard versus 13.3% reduced dose. Time to progression HR 1.17 (0.71-1.93) **Survival** 5yr survival= 84.25% standard, 20.57% reduced dose. HR death 1.08 (0.74-1.58) **Toxicity** Local toxicity Grade 1-2: 49% (n=124) standard dose; 48% (n=119) reduced dose Grade 3-4: 18% (n=44) standard dose; 7% (n=16) reduced dose Withdrawn from study: 9% (n=23) standard dose; 4% (n=10) reduced dose.	
Oddens 2012	Randomised trial 1997 to 2005	1355 Median age 68 (29 to 85) 81% M/ 18% F	N (%) Primary: 793 (58.5) Recurrent: 553 (40.8) No. of tumours Single: 179 (13.2) Multiple: 1163 (85.8)	BCG: One-third dose with 1yr maintenance, vs. One-third dose with 3yr maintenance, vs. Full-dose-1yr	4 trial arms	Median 7.1yrs, maximum 13.5yr	**Disease-free interval** 1/3D for 1 yr is suboptimal compared with FD-3yr HR 0.75 (0.59-0.94) In intermediate risk patients 3-yr of maintenance was more effective than 1 yr in patients	Intent-to-treat analysis performed. Toxicity to be reported in separate paper.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			T category T0: 3 (0.2) Ta: 852 (62.9) T1: 493 (36.4) T2: 2 (0.1) Grade (WHO 1973) G0: 1 (0.1) G1: 387 (28.6) G2: 598 (44.1) G3: 361 (26.6) Risk group Intermediate: 789 (58.2) High: 560 (41.3) Unknown: 6 (0.4)	maintenance, vs. Full-dose-3-yr maintenance OncoTICE strain $5x10^8$ CFU. 1/3 dose dissolved in saline. Patients randomised within 14 days of TUR			receiving 1/3dose (HR 1.35, 1.03-1.79) but not in patients receiving full dose (HR 0.88, 95% CI, 0.64-1.21) In high-risk patients, 3 yr maintenance was more effective than one year in patients receiving full dose (HR 1.61, 1.13-2.30), but not with 1/3 dose (HR1.01, 0.69-1.47) **Progression and survival** No differences between groups **Toxicity** No medically significant differences between treatment groups. Cystitis 56%, haematuria 46%, frequency 45%. Neither reducing the dose nor shortening the duration of maintenance decreased the % of patients who discontinued treatment due to side-effects.	
Houghton 2012	Systematic review of randomised trials published 1999 to 2008	801 patients from 4 trials	All trials included patients with T1 disease, 3 included Ta and one included Tis.	Sequential chemotherapy and BCG (each trial used different doses and schedules)	BCG alone (6 months maintenance BCG required in both arms)	Range 15 to 88 mo	**Recurrence** 173/412 (42%) combined therapy vs. 178/389 (46%) BCG only (RR 0.92, 95% CI 0.79-1.08). MA showed substantial heterogeneity **Progression** RR 0.88 (95% CI 0.61-1.27) Subgroup analyses showed benefit of combined therapy for Ta/T1 disease and not for Tis **Toxicity** Two studies reported toxicity data. No differences in cystitis, haematuria, fever between	Kaasinen 2003; Ali-El-Dein 1999; Cai 2008; Di Stasi 2006

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Included studies</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>groups.</td><td></td></tr>
<tr><td>Oosterlinck 2011</td><td>Randomised trial 2001 to 2005</td><td>96 CIS randomised, 83 eligible patients started treatment</td><td><table>
<tr><td></td><td>N (%)</td></tr>
<tr><td>Median age</td><td>69</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Male</td><td>83 (86.5)</td></tr>
<tr><td>Female</td><td>12 (12.5)</td></tr>
<tr><td>WHO PS</td><td></td></tr>
<tr><td>PS0</td><td>90 (93.8)</td></tr>
<tr><td>PS1</td><td>5 (5.2)</td></tr>
<tr><td>Type of CIS</td><td></td></tr>
<tr><td>No CIS</td><td>9 (9.4)</td></tr>
<tr><td>Primary</td><td>32 (33.3)</td></tr>
<tr><td>Secondary</td><td>8 (8.3)</td></tr>
<tr><td>Concurrent</td><td>46 (47.9)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Papillary lesions</td><td></td></tr>
<tr><td>No</td><td>42 (43.8)</td></tr>
<tr><td>Yes</td><td>53 (55.2)</td></tr>
<tr><td>pTa</td><td>28</td></tr>
<tr><td>pT1</td><td>24</td></tr>
<tr><td>pTx</td><td>1</td></tr>
</table></td><td>Weekly MMC 40mg for 6 wks followed by 6 weekly TICE BCG

Maintenance treatment was 1 instillation MMC followed by 2 BCG instillations weekly.</td><td>6 weekly TICE BCG followed by 3 wk rest then 3 wk BCG

1st instillation 15-28days after TUR. Complete responders had 3-weekly maintenance at 6,12,18,24, 30, 36 months</td><td>Median 4.7 yr, max 6.5yr</td><td>Recurrence
23/48 (47.9%) MMC+BCG vs. 26/48 (54.2%) BCG (ns)

Progression
2/48 MMC+BCG vs. 5/48 BCG

5-yr overall survival
82.7% MMC+BCG vs. 77.8% BCG

Toxicity
16% cystitis, 24% dysuria, 26% frequency, 1 patient BCG sepsis. No differences between groups.</td><td>Randomisation not for purpose of treatment comparison. No formal treatment comparisons made and no p values given for any end-points.</td></tr>
<tr><td>Mack 1996 Austria</td><td>Cross-sectional study</td><td>85 with superficial disease</td><td>Mean age 59 years, range 26-85. 64 men and 21 women. 79% high risk (T1/G3 and Tis), 21% intermediate risk (Ta-T1/G1-2). All underwent BCG low-dose 6-weekly instillations followed by maintenance therapy once-monthly for first year and 3-monthly for 2nd year</td><td>QoL questionnaire inc. Questions about psychology, symptoms, sexual activity, and general QoL. Completed at start of treatment and twice during maintenance</td><td>N/A</td><td>N/A</td><td>Physical symptoms
Comparable during initial and maintenance therapy (40%). Micturation problems also comparable (84% at start 80% 3-mo maintenance)
44% showed reduced activity level at start of treatment, 13% during 3-mo instillations
22% of patients reported disruption to sex life during initial cycle of therapy, which decreased to 13% during maintenance.
Overall quality of life and condition of health was only moderate in 69% and 71% at initial treatment but both</td><td></td></tr>
</table>

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Included studies</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>improved during 3-mo maintenance. The burden of accepting the diagnosis of bladder cancer was high in around 70% of patients (involving fear of recurrence or death) despite being told their cancer was superficial and curable.</td><td></td></tr>
<tr><td>Bohle 1996

Germany</td><td>Cross-sectional study</td><td>30 patients with superficial disease</td><td>5 female, 25 male. Ta/T1 Grade 1-3. Average patient age = 67±11.4 years.

All received 150mg Connaught BCG 6=weekly instillations and no maintenance</td><td>QoL & side effects questionnaire completed during and after BCG therapy. MLDL questionnaire</td><td>N/A</td><td>N/A</td><td>General satisfaction with life (average 84 points, range 1-100) No differences before, during and after BCG). No changes in state of health (average 4.8, range 1-7)
Side effects (micturition and haematuria) increased on the first 2 days after instillation and decreased thereafter. Mean subjective evaluation of the side effects during instillation was rated as moderate. No patient rated the side effects as too severe during treatment. Incidence of side effects correlated well with QoL.</td><td></td></tr>
<tr><td>Badalament 1987

USA</td><td>Randomised trial
1981-1984</td><td>93 patients with recurrent superficial bladder cancer</td><td><table><tr><th></th><th>Maint</th><th>No Maint</th></tr><tr><td>Median age</td><td>62</td><td>63.5</td></tr><tr><td>Male</td><td>41 (87%)</td><td>40 (87%)</td></tr><tr><td>Female</td><td>6 (13%)</td><td>6 (13%)</td></tr><tr><td>Prior IV chemo</td><td>13 (28%)</td><td>11 (24%)</td></tr><tr><td>CIS</td><td>36 (77%)</td><td>36 (78%)</td></tr><tr><td>Persistent tumour after BCG</td><td>16 (34%)</td><td>17 (37%)</td></tr></table></td><td>120mg Pasteur BCG 6-wk induction plus maintenance BCG – single dose 120mg monthly for 2yr</td><td>6-wk induction only</td><td>Median 22 months</td><td>Recurrence-free interval
22 months no maintenance vs. 20 months maintenance (p=0.80, ns)
Progression
12 (26%) progressed in maintenance arm vs. 9 (20%) non-maintenance (ns).
No deaths reported on either arm.
Toxicity
Maintenance – 42 (89%) dysuria, 40 (85%) frequency, 27 (57%) haematuria, 20 (43%) fever</td><td>Method of randomisation, allocation concealment and blinding not reported</td></tr>
<tr><td>Hudson 1987</td><td>Randomised trial</td><td>42 patients with NMIBC.</td><td></td><td>120mg Pasteur BCG 6-wk</td><td>6-wk induction</td><td>Mean 16</td><td>Recurrence
6 (29%) no maint vs. 5 (24%)</td><td>Small sample size.</td></tr>
</table>

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Included studies</th></tr>
<tr><td>USA</td><td></td><td>Excluded patients who failed treatment</td><td></td><td>induction plus maintenance every 3 months</td><td>only</td><td>months</td><td>maint (ns). Time to recurrence 17.2 mo vs. 14.6 mo
Toxicity
Dysuria 67% v 81% (ns)
fever/chills 29% v 33% (ns)
Haematuria 5% both groups</td><td>Short follow-up</td></tr>
<tr><td>Palou 2001
Spain</td><td>Randomised trial
1989-1995</td><td>126 patients primary or recurrent Ta/T1 Grade3 with or without CIS</td><td><table><tr><th></th><th>Maint</th><th>No Maint</th></tr><tr><td>Mean age</td><td>65</td><td>63</td></tr><tr><td>Male</td><td>64</td><td>58</td></tr><tr><td>Female</td><td>1</td><td>3</td></tr><tr><td>Primary</td><td>46</td><td>43</td></tr><tr><td>Recurrent</td><td>19</td><td>18</td></tr><tr><td>Solitary</td><td>24</td><td>25</td></tr><tr><td>Multiple</td><td>29</td><td>28</td></tr><tr><td>Ta High grade</td><td>16</td><td>14</td></tr><tr><td>T1high grade</td><td>25</td><td>27</td></tr><tr><td>Ta low grade</td><td>6</td><td>5</td></tr><tr><td>Ta high grade</td><td>6</td><td>7</td></tr><tr><td>Solitary CIS</td><td>12</td><td>8</td></tr></table></td><td>81mg Connaught BCG 6-wk induction plus maintenance 6-weekly every 6mo for 2 yrs

34% completed 2-yr treatment. 32 stopped due to intolerance</td><td>6-wk induction only

Relapses treated with further BCG</td><td>Median 77.8 months</td><td>Recurrence
16/61 (26.2%) in control and 10/65 (15.4%) maintenance arm at a mean of 24 and 20 months (p=0.07).
Progression
2/61 (3%) control vs. 3/65 (4.6%) maintenance
Overall mortality
8/61 (13.1%) control vs. 11/65 (16.9%) maintenance (ns)</td><td>ITT analysis performed</td></tr>
<tr><td>Lamm 2000

USA</td><td>Randomised trial
1985-1988</td><td>384 recurrent and/or CIS patients disease-free after induction BCG. Previous iv chemo allowed</td><td><table><tr><th></th><th>Maint</th><th>No Maint</th></tr><tr><td>N patients</td><td>192</td><td>192</td></tr><tr><td>Male</td><td>159 (83%)</td><td>173 (90%)</td></tr><tr><td>Mean age</td><td>67</td><td>67</td></tr><tr><td>CIS</td><td>66 (34%)</td><td>64 (33%)</td></tr></table></td><td>81mg Connaught BCG 6-wk induction plus maintenance 3-wk at 3& 6 months, then every 6 mo up to 3yrs.
Intravesical and percutaneous BCG

Only 16% (out of 243) received all 8 maintenance courses during 3 years</td><td>6-wk induction only</td><td>7 years</td><td>Recurrence
142/192 (73.9%) no maintenance vs. 108/192 (56.3%) maintenance
5-year RFS=41% v 60% (p<0.0001)
Worsening-free survival
102/192 (53.1%) no maintenance vs. 87/192 (45.3%) maintenance
5-yr WFS = 70% vs. 76% (p=0.04)
Survival
93/192 (48%) no maintenance vs. 81/192 (42%) maintenance
5-yr survival 78% vs. 83% (p=0.08)
Toxicity
2 BCG related deaths due to systemic infection out of 599 patients evaluated for induction period toxicities. No toxicities above G3 in maintenance arm.</td><td></td></tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
Koga 2010 Japan	Randomised trial 2002-2005	53 patients with Ta/T1 or CIS who had CR after induction therapy	<table><tr><td></td><td>N. patients</td></tr><tr><td>Enrolled</td><td>90</td></tr><tr><td>Evaluable</td><td>84</td></tr><tr><td>Male</td><td>68</td></tr><tr><td>Female</td><td>16</td></tr><tr><td><70yrs old</td><td>39</td></tr><tr><td>>70 yrs old</td><td>45</td></tr><tr><td>Primary</td><td>60</td></tr><tr><td>Recurrent</td><td>24</td></tr><tr><td>PS 0</td><td>80</td></tr><tr><td>PS 1,2</td><td>4</td></tr><tr><td>CIS</td><td>74</td></tr><tr><td>Ta, T1</td><td>10</td></tr><tr><td>Smoking</td><td></td></tr><tr><td>No</td><td>28</td></tr><tr><td>Yes</td><td>56</td></tr></table>	80mg Tokyo BCG 8-wk induction plus maintenance single instillation every 3 months x4 (max 12 doses) 75% received all 4 doses	8-wk induction only	Median 26.5 mo maintenance and 28.7 mo control	**Recurrence** 1/24 (4%) maintenance vs. 7/27 (26%) control. 2-year RFS = 95.8% maintenance and 74.1% control (p=0.078) **Progression** 0/24 maintenance vs. 1/27 control (ns) **Survival** 2/24 maintenance vs. 2/27 control (ns) 2-yr overall survival – 91.7% vs. 92.6% (p=0.885) **Toxicity** 82.2% had urination-related local symptoms. 30% pyrexia during induction. 21% frequency and 17% pain on urination during maintenance. These adverse events resolved with/without anti-inflammatory agents. **QoL** EORTC-QLQ-C30 In both groups none of the functioning or symptom scales showed a significant change in QoL after randomisation compared with before.	Funded by Japan BCG laboratory
Hinotsu 2010 Japan	Randomised trial 2004-2006	116 patients (83 with BCG) recurrent or multiple Ta/T1 No iv therapy within 12 mo prior to study entry. CIS excluded	<table><tr><td></td><td>BCG</td><td>Epirubicin</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Ta</td><td>58</td><td>24</td></tr><tr><td>Ta</td><td>25</td><td>8</td></tr><tr><td>≤64 yrs</td><td>39</td><td>11</td></tr><tr><td>≥65 yrs</td><td>44</td><td>21</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Male</td><td>73</td><td>31</td></tr><tr><td>Female</td><td>10</td><td>1</td></tr><tr><td>Previous BCG</td><td></td><td></td></tr><tr><td>No</td><td>77</td><td>29</td></tr><tr><td>Yes</td><td>6</td><td>3</td></tr><tr><td>G1</td><td>15</td><td>4</td></tr></table>	81mg Connaught BCG 6-wk induction plus maintenance 3-wks at 3,6,12 and 18 mo 42% completed therapy at 18 mo	6-wk induction only 3rd arm – Epirubicin 40mg, every wk x2 then every 2 wks x7	4-years	**Recurrence** 14/42 (33.3%) no maintenance vs. 5/41 (12.2%) maintenance vs. 22/32 (68.8%) epirubicin. 2-yr RFS better in combined BCG compared with EPI 33.2% (p<0.0001). Maintenance 92.7% versus non-maintenance 65.4% (p=0.02) **Progression** 3/42 (7.1%) maintenance vs.	Funded by licence holder for Connaught BCG in Japan. Trial terminated early due to significant interim analysis.

Study, country	Study type, study period	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
			G2	53	21				0/41 (0%) maintenance vs. 7/32 (21.9%) EPI. BCG vs. EPI (p=0.0047). M BCG vs. EPI (p=0.002). M vs. no M (p=0.24) **Toxicity** Adverse events lower in EPI group compared with BCG. Higher in maintenance compared with non-maintenance. All controlled by suspending treatment or administering anti-inflammatory or analgesic therapy	
			G3	15	7					
			Recurrent/ multiple	41	15					
			Primary/ multiple	36	13					
			Recurrent/ solitary	6	4					
			Intermediate risk	72	25					
			High risk	11	7					

Health Economic Evidence: What are the comparative patient outcomes for treating low-risk non-muscle invasive bladder cancer with: Intravesical chemotherapy

Background

Non-muscle invasive bladder cancer (NMIBC) tumours can be surgically removed using transurethral resection of bladder tumour (TURBT). However, these tumours are likely to return on the urothelium. This high risk of recurrence is a problem for patients because it raises the concern that the cancer will progress and so the patient will need to undergo further treatment (either another TURBT or diathermy).

The risk of recurrence can be reduced by the administration of chemotherapy medication into the bladder (intravesical chemotherapy), which can be done immediately, or shortly after TURBT. However, there are disadvantages to using intravesical chemotherapy as it is associated with some side effects and comes at an additional cost.

Aim of analysis:

To estimate the cost-effectiveness of a single instillation of intravesical chemotherapy in addition to TURBT in comparison to TURBT alone in patients with NMIBC.

Existing Economic Evidence

A systematic literature review identified one paper related to the decision problem, a cost-utility analysis by Green et al. 2013. In the study, a decision analytic model was utilised to estimate the cost-effectiveness of fulguration compared to TURBTs with and without perioperative intravesical chemotherapy in patients with low risk NMIBC.

The authors concluded that fulguration without perioperative intravesical chemotherapy was the most cost-effective strategy for treating low-risk NMIBC. However, unusually, the authors based this conclusion upon individual cost-effectiveness calculations rather than the standard incremental calculations. When following the more standard cost-effectiveness methodology using incremental cost-effectiveness ratios (ICERs), it appears that perioperative intravesical chemotherapy plus fulguration would be the most cost-effective strategy. This strategy has an ICER of $4,169 per QALY, which is likely to fall below the cost-effectiveness threshold[3]. The authors also conducted sensitivity analysis, which showed that the effectiveness of perioperative intravesical chemotherapy and the cost of TURBT were likely to be key drivers of the cost-effectiveness result.

However, Green et al. 2013 can only be deemed partially applicable to the decision problem this guideline seeks to address. The analysis considered the US healthcare system, which differs substantially from the UK system. In addition, the study only partially addressed our decision problem as it only evaluated cost-effectiveness in low risk NMIBC patients, whereas we are interested in all NMIBC risk groups.

[3] However, it should be noted that there is no official cost-effectiveness threshold used in the evaluation of treatments in the US health care system.

Overall, it was considered that the current economic literature was partially useful but further analysis would be required to robustly estimate the cost-effectiveness. It should also be noted that the existing economic literature was useful for informing the development of our own economic model.

De Novo Economic Model

Since the current economic literature did not adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel.

The patient enters the model in a 'disease free' state following an initial transurethral resection of the bladder tumour (TURBT) with or without a single instillation of chemotherapy (depending upon modelled treatment arm). At each 3-monthly model cycle the patient may experience a bladder cancer recurrence. If the recurrence is detected, the patient will undergo a further TURBT (or fulguration of the tumour) and return to a disease free state. However, if the recurrence is not detected, then the patient will be at risk of progression and will have to undergo further treatment once this progression is eventually detected (cystectomy and possibly neo-adjuvant chemotherapy). The patient may also die from bladder cancer related mortality after experiencing progression and may die from other cause mortality from any health state.

Estimated total costs and quality adjusted life yefars (QALYs) are collected over the modelled 10 year time horizon for each follow-up strategy. Future costs and benefits were discounted at a rate of 3.5% per year as recommended by NICE.

The risk of recurrence and progression in patients with NMIBC was estimated using risk equations based on an analysis of 2,596 patients from seven EORTC[4] trials (Sylvester et al. 2006). Patients are 'scored' based on a number of risk factors, such as number of tumours, tumour size, prior recurrence rate, T category, presence of CIS and grade. An individual's one year and five year risks of recurrence and progression can then be estimated based upon these scores.

For the purposes of the economic model, it was necessary to convert these five year and one year risks into 3-monthly risks. The higher risk of recurrence and progression in the first year was captured by calculating separate 3 monthly risks for the first year and subsequent years (based on the one year risk and five year EORTC risks). Furthermore, since the EORTC risk equations consider recurrence and progression *independently*, it was necessary to link the progression rates to the recurrence rate i.e. estimate the *probability of progression given recurrence* in each of the risk groups.

Table 66: Three Monthly Recurrence And Progression Risk Applied In The Model

Outcome	3 monthly rates		
	Recurrence	Progression given recurrence	Progression
First year			
Low risk	3.98%	1.26%	0.05%

[4] European Organisation for Research and Treatment of Cancer

Outcome	3 monthly rates		
	Recurrence	Progression given recurrence	Progression
Intermediate risk	6.63%	3.78%	0.25%
High risk – Lower	11.26%	11.31%	1.27%
High risk – Upper	20.97%	21.70%	4.55%
Subsequent years			
Low risk	1.84%*	2.18%*	0.04%*
Intermediate risk	3.03%	10.18%	0.31%
High risk – lower	4.72%	19.64%	0.93%
High risk – upper	7.29%	40.39%	2.94%

*In low risk patients, rates of recurrence and progression in years 6-10 are assumed to be zero

As the modelled time horizon of 10 years exceeds the predicted risk estimates from the EORTC trials (5 years), it was also necessary to make some assumptions about the risk profile of patients in years 5-10. In the base case, it was assumed that the subsequent year rate (i.e. years 2-5) would be maintained in years 6-10 except in the case of low-risk patients in whom it was assumed that risk would be zero after 5 years (reflecting clinical practice of discharging low-risk patients from follow-up after 5 years).

The key effectiveness data utilised in the model is the reduction in recurrence risk associated with a single instillation of intravesical chemotherapy following a TURBT. According to the systematic review of the clinical evidence, the use of a single instillation of intravesical chemotherapy in addition to TURBT has a relative risk of 0.67 in comparison to TURBT alone. This treatment effect was assumed to last for two years reflecting the general consensus around its possible duration. Thereafter, the risk of recurrence was assumed to be equal to that with TURBT only. In addition, the treatment effect is not assumed to affect future recurrences if the patient has a recurrence during the two years after the single chemotherapy instillation.

Note that the single instillation of chemotherapy does not directly reduce the rates of progression. This is in line with the evidence base, which suggests that there is no treatment effect on the rates of progression. However, it should be noted that because of the model structure, a lower rate of recurrences would lead to a lower rate of progression because progression is dependent upon recurrence. Therefore, an indirect treatment effect on progression is essentially included in the model. This assumption is relaxed in a sensitivity analysis where the rates of recurrence and progression are assumed to be independent.

No comparative data on morbidity were identified in the systematic review of the clinical evidence. However a meta-analysis (Sylvester 2004) of seven trials suggested that mild irritative bladder symptoms (including dysuria, frequency and macroscopic haematuria) would occur in approximately 10% of patients treated with a single post-operative dose of intravesical chemotherapy. In addition, allergic skin reactions were reported in 1-3% of patients in two studies.

Since no data were available on morbidity in patients treated with TURBT, it was conservatively assumed that 5% would have irritative bladder symptoms and there would be no skin reactions. The treatment related morbidity rates applied in the model are shown in the table below.

The diagnostic accuracy data for flexible cystoscopy were sourced from the systematic review of the clinical evidence conducted for this guideline, with most data being sourced from a systematic review by Mowatt et al. 2010.

Bladder cancer related mortality rates were estimated using data from a systematic review by Van den Bosch et al. 2011. Using the data in the study, separate three mortality rates were estimated for patients that progressed to muscle invasive disease and those that remained non-muscle invasive following a cystectomy (3.6% and 0.5%, respectively). The lower rate in NMIBC patients reflects an assumption that patients would have to first progress to MIBC before dying of bladder cancer.

Death from other causes was captured using 2009-2011 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender with the model assuming that 50% of patients were female and that the average age was 60 years old. These annual probabilities were converted to three-monthly probabilities for use in the model.

Costs and utilities

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. GP visit). Where possible, all costs were estimated in 2012-13 prices.

The majority of costs were sourced from NHS reference costs 2012/13 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dosages from the British National Formulary (BNF) and unit cost information from the electronic market information tool (eMit). Where unit costs for drugs were not available from eMit, prices from the BNF were used. Resource use and cost information were obtained from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs were estimated by combining the life year estimates with utility values (or QOL weights) associated with being in a particular health state. These utility values were identified through a search of the available literature.

Base case results

The base case results of the analysis are presented in the table below for patients in each risk category. It can be seen that, in every risk category, a strategy of TURBT plus a single instillation of chemotherapy is more effective than a strategy of TURBT alone.

In the case of low and intermediate risk patients, it can also be seen that the addition of a single instillation of chemotherapy is cost saving over the modelled time horizon. This shows that the initial additional costs associated with the single chemotherapy instillation are outweighed by the cost savings associated with a reduction in recurrences (recurrence reductions of 17% and 10% were estimated over the modelled time horizon in the low and intermediate risk groups, respectively).

Therefore in low and intermediate risk patients, a single instillation of chemotherapy can be considered dominant i.e. more effective and cost saving.

However, in the case of high risk patients, it can be seen that this is not the case. In high risk patients, the single instillation of chemotherapy is more costly than TURBT alone, suggesting that the potential cost savings are not as large in this group. However, it can also be seen that the addition of a single chemotherapy instillation provides an additional QALY at a cost of £6,432 and thus would be considered cost-effective using the NICE threshold (i.e. <£20,000 per QALY).

Table 67: Base Case Results Of The Model

Treatment strategy	Cost		QALYs		Cost per
	Total	Incremental	Total	Incremental	QALY
Low risk					
TUBRT alone	£8,850	-	6.29	-	-
TURBT + single chemo instillation	£8,203	-£647	6.30	0.0056	***Dominant***
Intermediate risk					
TUBRT alone	£21,992	-	6.20	-	-
TURBT + single chemo instillation	£21,191	-£801	6.22	0.0185	***Dominant***
High risk					
TUBRT alone	£27,679	-	5.52	-	-
TURBT + single chemo instillation	£28,069	£389	5.58	0.0605	***£6,432***

Sensitivity analysis

A series of one-way sensitivity analyses were conducted, whereby the value of an input parameter is changed and its effect on the overall outcome is recorded and assessed.

The analyses showed that the conclusion of the model is insensitive to changes in the input parameters over plausible ranges i.e. TURBT plus a single instillation of chemotherapy remains cost-effective in the all the analyses across all the risk groups.

The variations in the treatment effect duration are perhaps particularly notable as this is one of the uncertainties around the effectiveness of the single instillation of chemotherapy. The analysis shows, unsurprisingly, that the intervention is less cost-effective when the treatment effect duration is decreased. However, crucially, the single instillation of chemotherapy remains cost-effective in all analyses, even when making very pessimistic assumptions about the likely treatment effect duration (i.e. even when assuming that the chemotherapy instillation only reduces recurrences in the first 3 months after administration).

In addition to the core cost-utility analysis, the GDG were also interested in a cost analysis comparing the cost of delivering the single instillation of chemotherapy on the ward against the cost of delivering it in theatre. It was found that delivering the single instillation of chemotherapy in theatre was the cheaper of the two approaches (delivery by nurse estimated to cost an additional £23.83). This was primarily a result of the longer amount of time taken to deliver the instillation in the ward setting compared to in theatre.

A probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case were replaced with values drawn from distributions around the mean values. It was found that, at a threshold of £20,000 per QALY, TURBT plus a single instillation of chemotherapy has a very high probability of being cost-effective in the low and intermediate risk groups (100%). However, the probability is substantially lower in high risk patients at 66%, although still very much in favour of TURBT plus a single instillation of chemotherapy.

Conclusion

The results of the analysis suggest that the use of a single instillation of chemotherapy after a TURBT, in comparison to a TURBT alone, was found to be strongly cost-effective in all risk groups. It was found to be particularly cost-effective in low and intermediate risk groups, in which the strategy was cost saving as well as more effective (dominant). Furthermore, this result was found to be robust in alternative scenario analyses, one-way and probabilistic sensitivity analysis.

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3.2.2 The role of biopsy in people with recurrent non-muscle invasive bladder cancer

Review question: In patients with recurrent bladder cancer and previous low risk bladder cancer does treatment without histological sampling affect outcome?

Rationale

Treatment of low risk bladder cancer recurrences may be with endoscopic resection to remove the cancer, fulguration by electrocautery or laser energy to destroy the cancer in situ (with or without biopsy), intravescial chemotherapy (also known as chemoresection) or merely observation (so called active surveillance). The former allows pathological evaluation of the cancer and may be necessary to remove tissue from large tumors, but requires regional or general anaesthesia and a rigid cystoscopy and bladder resection. Consequently, the risks of intervention are higher than for fulguration (which may performed under local anaesthesia), chemotherapy or active surveillance. However, these other approaches do not sample the tissue of the cancer recurrence and could miss the minority of cases in which the cancer is becoming more aggressive. Also these approaches are less effective at removing the cancer and so could lead to higher recurrence (or residual cancers) rates and more post-treatment symptoms.

In this review we will evaluate each approach to treating recurrence within the bladder following a previous low risk bladder cancer. We will attempt to determine in which patients the benefits of transurethral resection outweigh the risks from the treatment and from the cancer. We will attempt to identify low risk cancers in which the rate of disease progression is higher and so the evaluation of tissue is necessary for patient safety. We will look to identify tumors in which less intensive intervention is sufficient and to compare the outcomes of the different approaches.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with recurrent bladder cancer and previous low risk NMIBC	Treatment with histological sampling e,g, cystocopy & biopsy or TUR	Treatment without histological sampling e.g cystodiathermy	• Recurrence • Progression • Residual tumour rate • Treatment-related morbidity • Health-related quality of life, inc patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. Comparative evidence was looked for, but only one study was identified. Therefore, evidence from non-comparative observational studies was included.

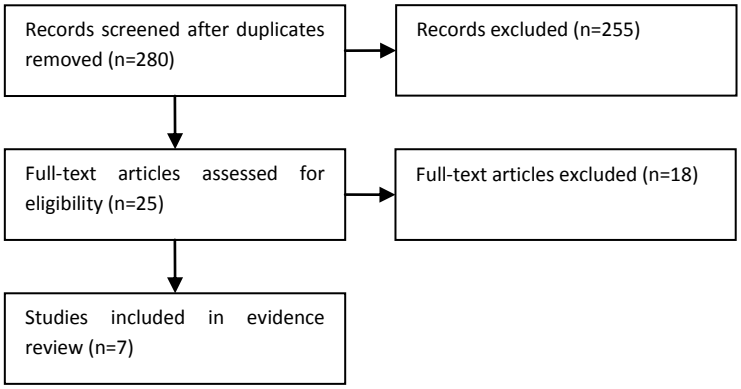
Data synthesis

Data was presented using GRADE. Meta-analysis was not possible for this review question.

RESULTS

Result of the literature searches

Figure 49. Study flow diagram



Study quality and results

Very low quality evidence was obtained from seven observational studies. Evidence is presented in Table 68.

Evidence statements

Very low quality evidence from one retrospective observational study reported on 42 patients who underwent fulguration for recurrent Ta bladder cancer and 42 matched patients who underwent TURBT. 12 patients in the fulguration group and 11 patients in the TURBT group had a recurrence during follow-up (RR 0.92, 95% CI 0.46 to 1.84) (Park *et al.*, 2013).

Very low quality evidence from one prospective cohort study of outpatient laser ablation (OLA) in an elderly population (n=54) reported that the procedure was well tolerated with pain scores of 0-2 out of 10. The 3-month recurrence rate was 10.6% with white light OLA and 4.3% with PDD OLA (Wong *et al.*, 2013).

One study of electromotive drug administration (EMDA) of local anaesthetic (LA) for outpatient flexible cystoscopy biopsy and cystodiathermy of recurrent low grade pTaG1-2 (Biers *et al.*, 2009) reported that there were no recurrences at the site of cystodiathermy and there were no progression events. 19% (3/16) of those with benign pathology at biopsy had a recurrence after a

mean follow-up of 16.4 months. 9% (1/11) of those with TCC pathology at biopsy had a recurrence, with a time to recurrence of 15 months. Mean pain score was one, on a scale of one (no pain) to 10 (worst pain). There were no intraoperative complications (Very low quality evidence).

One study of 48 patients who were suitable for cystodiathermy under LA reported a local recurrence rate of 6% (n=3) and 15 recurrences (31%) at a different site after a median of 15 weeks follow-up (80% subsequently treated with LA cystodiathermy and 20% referred for GA cystodiathermy). No progressions were reported (Davenport *et al.*, 2004) (Very low quality evidence).

Two studies of 192 patients (515 tumours) undergoing treatment for NMIBC recurrences with Ho:YAG laser ablation under LA with a flexible cystoscope reported a local recurrence rate of 12% (37/304) and an off-site recurrence rate of 50% (Syed *et al.* 2001; 2013). One study (Syed *et al.*, 2013) reported complication rates of dysuria (4.2%), frequency (1.5%), haematuria (1.9%) and no UTIs. Mean visual pain score was one, on a scale of 0 (no pain) to 10 (worst pain) (Very low quality evidence).

In one study of 267 patients, 103 had small, low grade papillary recurrence and negative cytology and underwent office cystodiathermy at least once during the study period (Donat *et al.*, 2004). No significant differences were seen in progression of disease for patients undergoing cystodiathermy (n=103) compared to those never fulgurated in the office (n=164) (p=0.86) (Very low quality evidence).

Table 68. GRADE evidence profile: Treatment with histological sampling versus treatment without histological sampling (e.g. cystodiathermy)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Histological sampling	Cystodiathermy	Relative (95% CI)	Absolute	
Recurrence rate (TURBT versus Fulguration) (follow-up median 27.8 and 25.1 months)											
1[1]	observational studies	none	none	none	serious[2]	none	11/42 (26.2%)	12/42 (28.5%)	RR 0.92 (0.46 to 1.84)		⊕OOO VERY LOW
Recurrence rate at 3 months (outpatient laser ablation (OLA) without PDD versus OLA with PDD)											
1[3]	observational studies	none	none	none	serious[2]	none	10.6%	4.3%	-	-	⊕OOO VERY LOW
Recurrence rate (EDMA LA biopsy and cystodiathermy), Subgroup: No pathology possible (follow-up mean 12.7 months)											
1[4]	observational studies	none	none	none	serious[2]	none	0/6 (0%)	-	-	-	⊕OOO VERY LOW
Recurrence rate (EDMA LA biopsy and cystodiathermy), Subgroup: Benign pathology (follow-up mean 16.4 months)											
1[4]	observational studies	none	none	none	serious[2]	none	16/27 (59.3%)	-	-	-	⊕OOO VERY LOW
Recurrence rate (EDMA LA biopsy and cystodiathermy), Subgroup: TCC pathology											
1[4]	observational studies	none	none	none	serious[2]	none	1/11 (9.1%)	-	-	-	⊕OOO VERY LOW
Local recurrence rate (cystodiathermy) (assessed by: recurrence at same site treated by cystodiathermy; follow-up mean 15 weeks)											
1[5]	observational studies	none	none	none	serious[2]	none	-	3/48 (6.3%)	-	-	⊕OOO VERY LOW
Recurrence at untreated area (cystodiathermy) (follow-up mean 15 weeks)											
1[5]	observational studies	none	none	none	serious[2]	none	-	15/48 (31.3%)	-	-	⊕OOO VERY LOW
Local recurrence rate (Ho:YAG laser) (assessed by: recurrence at treated site)											
2[6]	observational studies	none	none	none	serious[2]	none	-	37/304 (12.2%)	-	-	⊕OOO VERY LOW
Recurrence at untreated area (Ho:YAG laser)											
2[6]	observational studies	none	none	none	serious[2]	none	-	111/222 (50%)	-	-	⊕OOO VERY LOW
Progression (follow-up median 2.6 years; assessed with: Increase in clinical stage or metastases)											
1[7]	observational studies	none	none	none	serious[8]	none	N=164	N=103	(p=0.860)[9]		⊕OOO VERY LOW
Residual tumour rate											
0	No evidence										

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Histological sampling	Cystodiathermy	Relative (95% CI)	Absolute	
	available										
Treatment-related morbidity EDMA LA biopsy and cystodiathermy (assessed with: Median pain score, scale 0 (no pain) to 10 (worst pain))											
1[4]	randomised trials	none	none	none	serious[2]	none	Mean score =1	-	-	-	⊕OOO VERY LOW
Treatment-related morbidity Ho:YAG laser (assessed with: Dysuria, frequency, haematuria, microbiological UTIs)											
1[10]	observational studies	none	none	none	serious[2]	none	-	4.2% dysuria, 1.5% frequency, 1.9% haematuria, 0 UTIs	-	-	⊕OOO VERY LOW
Treatment-related morbidity (outpatient laser ablation) (assessed with pain score, scale 0 (no pain) to 10 (worst pain)											
1[3]	observational studies	none	none	none	serious[2]	none		Pain score 0-2 in all 54 patients			⊕OOO VERY LOW
Health related quality of life											
0	No evidence available										

[1] Park 2013
[2] Low number of events limits precision.
[3] Wong 2013
[4] Biers 2009
[5] Davenport 2004
[6] Syed 2001; Syed 2013
[7] Donat 2004
[8] Small sample size limits precision. Number of events not reported.
[9] No differences in progression for cystodiathermy versus those never fulgurated in office
[10] Syed 2013

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Syed, HA et al. Flexible cystoscopy and Holmium:Yttrium aluminum garnet laser ablation for recurrent nonmuscle invasive bladder carcinoma under local anesthesia. Journal of Endourology 2013; 27(7): 886-891.

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Wong, KA et al. Outpatient laser ablation of non-muscle-invasive bladder cancer: is it safe, tolerable and cost-effective? BJU International 2013; 112(5): 561-567.

References to excluded studies (with reasons for exclusion)

de la Pena, E et al. Safety and efficacy of an active surveillance program in recurrent non-muscle invasive bladder tumors. Results of an extended series. European Urology, Supplements 2012; 11(1): e1041-e1041a.

Reason: not relevant to PICO

de la Pena, E et al. Oncological safety of an active surveillance program in recurrent non muscle-invasive bladder tumor. Journal of Urology 2013; 189(4 SUPPL. 1): e731

Reason: not relevant to PICO

Soloway, MS, Bruck, DS, and Kim, SS. Expectant management of small, recurrent, noninvasive papillary bladder tumors. Journal of Urology 2003; 170(2:Pt 1): t-41.

Reason: not relevant to PICO

Herr, HW, Donat, SM, and Reuter, VE. Management of Low Grade Papillary Bladder Tumors. Journal of Urology 2007; 178(4): 1201-1205.

Reason: not relevant to PICO

Gofrit, ON and Shapiro, A. Active surveillance of low grade bladder tumors. Archivio Italiano di Urologia, Andrologia 2008; 80(4): 132-135.

Reason: not relevant to PICO

Linton, KD et al. Disease specific mortality in patients with low risk bladder cancer and the impact of cystoscopic surveillance. Journal of Urology 2013; 189(3): 828-833.

Reason: not relevant to PICO

Finch, WJG, Habib, MR, and Banerjee, GK. Holmium laser ablation of recurrent superficial bladder tumours under topical anaesthesia using a flexible cystoscope in anticoagulated patients. European Urology, Supplements 2009; 8(4): 374

Reason: abstract only, unclear if population relevant to PICO

Hernandez, V et al. Safety of active surveillance program for recurrent nonmuscle-invasive bladder carcinoma. Urology 2009; 73(6): 1306-1310.

Reason: not relevant to PICO

Pruthi, RS et al. Conservative management of low risk superficial bladder tumors. Journal of Urology 1990; 179(1): 87-90.

Reason: not relevant to PICO

Gofrit, ON et al. Watchful waiting policy in recurrent Ta G1 bladder tumors. European Urology 306; 49(2): 303-306.

Reason: not relevant to PICO

Zhang, Y, Denton, BT, and Nielsen, ME. Comparison of surveillance strategies for low-risk bladder cancer patients. Medical Decision Making 2013; 33(2): 198-214.

Reason: not relevant to PICO (health economics)

Gao, X et al. Thulium laser resection via a flexible cystoscope for recurrent non-muscle-invasive bladder cancer: initial clinical experience. BJU International 2008; 102(9): 1115-1118.

Reason: not relevant to PICO (all patients sampled)

Jonler, M, Lund, L, and Bisballe, S. Holmium : YAG laser vaporization of recurrent papillary tumours of the bladder under local anaesthesia. BJU International 2004; 94(3): 322-325.

Reason: outcomes not relevant to PICO

MacDonald, D, Jones, R, and Syed, H. A prospective study of the efficacy and tolerability of ambulatory holmium laser ablation of recurrent non-muscle-invasive transitional cell carcinoma with flexible cystoscope under local anaesthesia. Journal of Endourology 2009; 23: A128

Reason: abstract only, maybe same study as Syed (2013)

Chandrasekar, P et al. Efficacy of managing small recurrent bladder tumours by diathermy using the CYF-4 olympus flexible cystoscope under local anaesthesia as an office setup. Journal of Urology 2009; 181(4 SUPPL. 1): 639

Reason: abstract only

Siddiqui, M et al. The use of KTP laser for ablation of small, superficial transitional cell carcinoma of bladder in outpatient, office setting. Journal of Endourology 2009; 23: A67

Reason: abstract only

Sabir, EF. TaG1 bladder tumours: One third of all primary tumours and 80 % of all recurrent tumours can be treated in the office under local anaesthesia. European Urology, Supplements 2013; Conference(var.pagings): 1

Reason: abstract only

Liu, H et al. Comparison of the safety and efficacy of conventional monopolar and 2-micron laser transurethral resection in the management of multiple nonmuscle-invasive bladder cancer. Journal of International Medical Research 2013; 41(4): 984-992.

Reason: comparison not relevant to PICO

Evidence tables

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Donat 2004 USA	Prospective observational study 1998-2001	267 consecutive patients seen in outpatient clinic for routine surveillance cystoscopy	N (%) Male 199 (75.4) female 68 (25.5) Median age 69.1 yrs Median time from diagnosis 6.84 yrs Median time from last tumour 20.4 mo Previous IVT 175 (65.5) Previous UUT 37 (13.9) History CIS 161 (60.3) High risk recurrence 202 (75.7) Low risk recurrence 65 (24.3) Never smoked 58 (21.7) Smoking 35 (13.1) Quit 174 (65.2) High risk = history of moderate or high grade papillary tumours, any invasion or associated CIS. Low risk= low grade papillary tumours or papilloma with no invasion (Ta or less)	All patients considered for fulguration had completed initial treatment TUR, partial cystectomy and/or IVT and a minimum of 6 mo on surveillance without recurrence. Follow-up at regular intervals ranging from every 3mo to once yearly, included physical exam, flexible cystoscopy, and cytology. Criteria for fulguration were less than 5 low grade appearing papillary tumours, tumour <0.5cm, negative cytology, and patient desire. If cytology positive or suspicious regardless of grade then a formal bladder biopsy was performed. All patients with tumour recurrence with high grade, non-papillary, >5 tumours, or size >0.5cm. underwent TUR under GA. 16.2Fr Olympus visera cystovideoscope was used for surveillance cystodiathermy. Lidocaine jelly (2%) in urethra for LA. Eligible tumours fulgurated with 4Fr bugbee electrode placed through a 5Fr working port in the flexible scope using a diathermy generator at 8-10 watts.	No fulgaration	Median 2.6 years (range 0.96 to 3.77)	123 (46%) had 1 or more recurrence. 74 (60%) underwent cystodiathermy. 49 (40%) had TUR. Overall 103/267 (38.6%) had been fulgurated at least once since diagnosis. **Progression:** When stratified by risk of recurrence 202/267 (76%) at high risk with low grade papillary recurrences undergoing diathermy did not have a greater risk of progression than patients at high risk undergoing TUR (p=0.90) **Survival:** No differences in DSS or OS for patients undergoing cystodiathermy compared to those never fulgurated.	NR	Location of tumour recurrence not reported.
Davenport 2010	Prospective observational study	69 patients treated with cystodiathermy	Mean age 74 (32-95) Male 56 Female 24 Histology at presentation G1pTa/G2pTa 55	Cystodiathermy: Instillagel instilled into urethra of all patients before insertion of cystoscope. Antibiotics not routinely used and no perenteral sedation or analgesia was used. Suitable tumours	N/a	Median 15 weeks (range 10-42)	88% tolerated procedure very well, 12% completed treatment but found it painful.	NR	

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			G2-3 pTa: 6 G2pT1: 4 G3pT1: 4 G3pT2: 2 UUT: 4 CIS: 3 Recurrences (n) 1: 49 2-5: 22 >5: 9 Treatment LA cystodiathermy: 51 LA holmium: YAG laser: 2 GA cystodiathermy: 16 GA TURBT: 9 MMC: 2 Cystodiathermy tolerance Well tolerated: 45 Tolerated but painful: 6 Unable t o tolerate: 0	fulgurated with a size 4-Fr Wolf fine cystodiathermy electrode, placed through the working port of the flexible cystoscope. The Eschmann TD300 solid state electrosurgical unit was set for monopolar coagulation at 3.0. The diathermy plate was most commonly placed on the patients right proximal thigh unless contra-indicated and glycine was used as the irrigating fluid. Exclusion criteria: Recurrence in patients with a history of high-grade disease, tumours >1cm in diameter, multiple large recurrences or those recurrences in a location requiring significant deflection			**Recurrence (n=48):** 30 (63%) no recurrence, 15 (31%) recurrence at different site (80% subsequently treated with LA cystodiathermy and 20% referred for GA cystodiathermy). 3 (6%) recurred at the same site treated by cystodiathermy. Overall 4/48 (8%) undergoing LA cystodiathermy required hospital admission and a GA procedure. No progressions.		
Syed 2013 UK	Prospective observational study 2006-2011	151 consecutive patients with recurrent NMIBC after prior TURBT. Anticoagulation was not an exclusion criteria and was not stopped before	Mean age: 73 male: 77% female: 23% Primary tumour G1: 88 (58%) G2: 51 (34%) G3: 12 (8%) Ta: 116 (78%) T1: 35 (22%)	Holminum YAG laser: 17F video flexible cystoscope with 210^{o} /120^{o} deflection, using LA gel per urethra. Ciprofloxacin 500mg was given 30 mins before procedure. No additional analgesics required. Using normal saline irrigation, a 230 or 360µm laser fibre passed through working channel of cystoscope. Once the exophytic component has been treated, the base was vaporized. Biopsies not routinely taken.	n/a	Median 24 months (0-58)	**Local recurrence rate:** 10%. Of those who developed local recurrence 92% were successfully treated with further laser treatment. Only 2 patients required formal cystoscopy and diathermy under GA. **Off-site recurrence rate:** 73 (48%). Of these 203 recurrences	NR	

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
		treatment.					96% treated with laser. **Mean visual pain score (range 0-7):** 1 100% were pleased with procedure. One would have preferred the GA procedure. No bladder perforation or damage to flexible cystoscope.		
Biers 2009 UK	Prospective observational study	31 patients with	Previous history of G1-2pTa TCC who at follow-up flexi cystoscopy had suspicious red patch or 1-3 small tumours each <5mm were offered flexi cystoscopy, biopsy and cystodiathermy using EMDA LA. Mean age 71.5 (53-88).	EMDA LA biopsy and cystodiathermy: Each patient was catheterized. 150ml of 0.5% bupivacaine ad 1.5ml of 1/1000 epinephrine instilled into bladder. A coagulation electrode connected to a diathermy generator set by 10W coagulation. Biopsy was attempted in all cases followed by fulguration. Pathologist was blinded to the method of obtaining the biopsy.	n/a		**Recurrence:** no pathology possible (6/33, 18%) 0% recurrence after mean 12.7mo f/up. Benign pathology (16/27, 59%) 3/16 (19%) recurrence after mean 16.4 mo f/up. TCC pathology (11/27, 41%). 1/11 (9%) recurrence – time to recurrence 15 mo. **Progression:** None **Median pain score:** 1 (range 0-5) on scale of 0 (no pain) to 10 (worst pain ever). 2/31 said they would prefer a GA next time.	NR	

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							Treatment related morbidity: No intra-operative complications.		
Syed 2001 UK	Prospective observational study 1994-1997	41 with recurrent previously documented low grade TCC NMIBC <1cm	28 men, 13 female. Mean age 67 (47-87). 6 had grade 1 lesions, 35 had grade 2. All had previous TURBT and histologic diagnosis.	Holmium laser irradiation under LA. 5F urethral catheter was used. The tumour was treated first and after visible shrinkage, the base was also irradiated. After laser coagulation, all tumours were mapped onto bladder diagram for identification at follow-up. All were treated as day cases with flexible cystoscope, none required catheterisation or hospitalisation.	Also retrospectively analysed a subgroup of 10 patients who were previously treated with cystodiathermy and had HoYAG laser treatment during the study	Mean 14 mo (3 to 33 mo)	**Recurrence:** 13 (18%) local recurrences, 38 (53.5%) recurring in untreated area of the bladder during study period. Local recurrence rate was lower in laser treated group than cystodiathermy treated group, p=0.39 (ns) **Morbidity:** No intra-operative or delayed complications. **Patient reported outcomes:** 33/33 patients were satisfied. Only 2 would elect to have GA for further procedures. 28/33 scored pain as 2 or less (out of 10).	NR	
Park 2013	Retrospective cohort study 2001-2012	42 consecutive fulguration patients matched with 42 TURB patients. All	<table><tr><td></td><td>Fulguration</td><td>TURBT</td></tr><tr><td>Mean age</td><td>66.7±7.1</td><td>67.1±3.4</td></tr><tr><td>Male</td><td>34 (81)</td><td>36 (86)</td></tr><tr><td>Female</td><td>8 (19)</td><td>6 (14)</td></tr><tr><td colspan="3">Initial bladder tumour surgery</td></tr></table>	Fulguration (n=42): 10cc lidocaine. Antibiotics not routinely used, and no parenteral sedation or analgesia used. Wolf 19 Fr cystoscope. Specimens taken from all patients at the suspicious recurrence site using biopsy forceps,	Fulguration matched to a cohort of 42 Ta patients who had traditional TURBT by the	Median 27.8 months for fulguration. Median 25.1 months for TURBT	**Malignant tumours:** Fulguration n=22 (52%) versus TURBT n=31 (74%) **Complications:**	No conflicts of interest.	Groups matched by age, BMI, ASA score, and primary

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
		initial treatment for Ta tumour. Excluded T1 and MIBC, ≥1cm mass at recurrence and masses at more than 3 sites, less than 1 yr follow-up.	Low grade: 21% / 22% High grade: 21% / 20% Mean no. TURB: 1.3±1.6 / 1.7±0.9 BCG: 21 (50) / 20 (48)	and the bladder tumour fulgurated with a size 4 Fr Wolf fine electrode. Mean tumour size similar in two groups 0.54cm fulguration versus 0.61cm in TURBT group. All patients who had TURBT had spinal or general anesthesia and required hospital stay. None of the fulguration group had hospital stay.	same surgeon.		assessed with Clavien classification system. Grade 1-2: 4 with fulguration vs 6 with TURBT. Grade 3-4: 0 with fulguration vs. 1 with TURBT. **Recurrence:** 12 (28.5%) with fulguration vs. 11 (26.2%) with TURBT 8 (19%) at same site with fulguration vs. 9 (21.4%) with TURBT. No differences in recurrence-free survival (p=0.880)		tumour characteristics
Wong 2013	Prospective observational study 2008-2011	54 elderly frail patients and patients with multiple comorbidities, for whom GA would present a risk, and small volume recurrent tumours offered OLA.	Excluded first presentation of tumour, young age (<50y), large tumours (>3cm), tumours adjacent to bladder neck, MIBC, untreated UTI. Mean age 77 (range 52-95). Male:femal ratio 1.39:1. More than half had more than 3 comorbidities, Previous tumour histology ranged from G1pTa to T3, and all patients had low volume recurrence at time of OLA. 4/8 patients on warfarin stopped	Outpatient laser ablation: performed by one surgeon, assisted by a laser trained nurse. Aseptic technique 10ml instillagel administered before cystoscopy and a 16.5F flexible video cystoscope. Used to map bladder with white light. A holmium:YAG laser with 365- or 200-nm fibre at 0.6-0.8Js ebergy and rate of 10-15Hz used to ablate any tumours. Normal saline solution used as irrigation fluid. Patients asked to void before discharge. From 2009-2011 a subgroup underwent	White light versus PDD OLA 74 OLA procedures (44 WLC, 30 PDD) in 54 patinents	3 months	**Pain:** All scored 0-2 on a scale of 0 (no pain) to 10 (worst pain. **Complications:** One patient with multiple tumours not on warfarin, had haematuria after OLA which settled spontaneously and didn't need hospital admission. No other	No conflicts of interest	Comparison not relevant to PICO

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			taking it before procedure. Other 4 continued warfarin treatment.	PDD before OLA. In these patients 50ml Hexvix instilled 1hour before OLA. Voided before procedure and a PDD-enabled 16.5 F flexible cystoscope was used with white light then blue light. Additional tumours (seen in 21% of patients) under blue light and not WLC were noted.			complications. **Recurrence:** At 3 months 10.6% who had OLA had recurrence vs 4.3% who had OLA with PDD. At 1 yr, recurrence rate was 65.1% and 46.9% respectively.		

Health Economic Evidence: What are the comparative patient outcomes for treating low-risk non-muscle invasive bladder cancer with transurethral resection

Review questions

In patients with recurrent bladder cancer and previous low risk bladder cancer does treatment without histological sampling affect outcome?

Table 69: Pico Table For Treatment With And Without Histological Sampling In Patients With Recurrent Bladder Cancer And Previous Low Risk Bladder Cancer

Population	Intervention	Comparison	Outcomes
Patients with recurrent bladder cancer and previous low risk NMIBC	Treatment with histological sampling e,g, cystocopy & biopsy or TUR	Treatment without histological sampling e.g cystodiathermy	• Recurrence • Progression • Residual tumour rate • Treatment-related morbidity • Health-related quality of life, inc patient reported outcomes

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO
- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

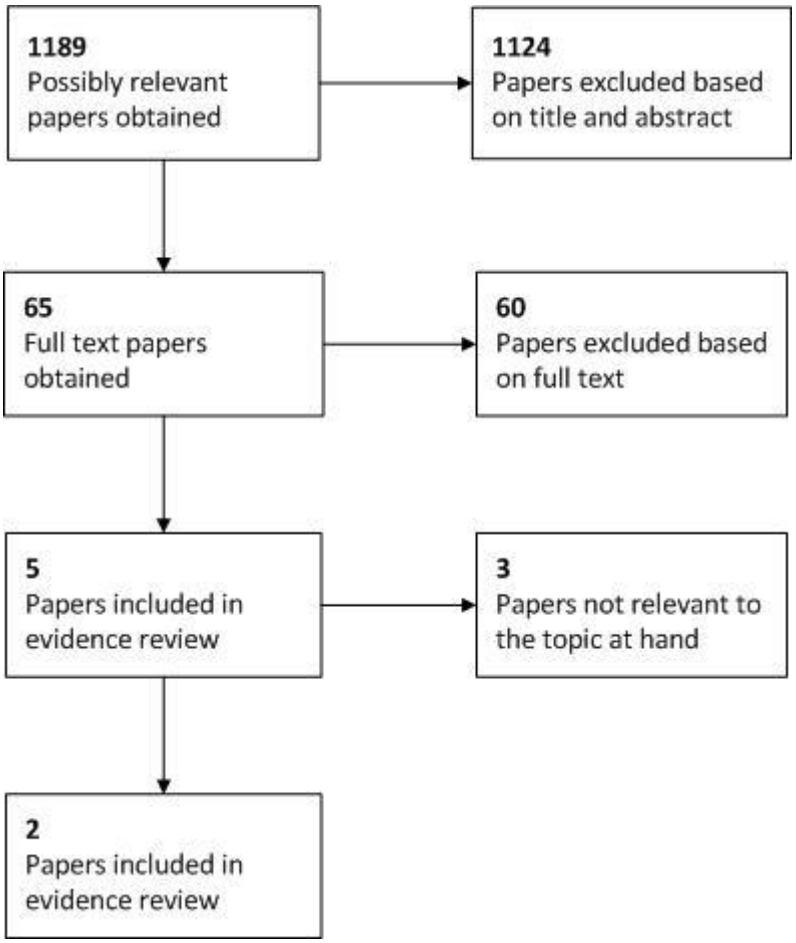
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

Three searches for economic evidence were run over the development of the guideline; one at the start of the process, an update midway through and a further update at the end of the process. The diagram below shows the combined results of the three searches and illustrates the sifting process.

Figure 50: Summary Of Evidence Search And Sifting Process For This Topic



It can be seen that, in total, 1,189 possibly relevant papers were identified. Of these, 1,124 papers were excluded at the initial sifting stage based on the title and abstract while 65 full papers were obtained for appraisal. A further 56 papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, nine papers were included in the systematic review of the economic evidence for this guideline.

Two of these nine papers related to the topic at hand and were thus included in the review of published economic evidence for this topic; Green et al. 2013 and Wong et al. 2013. The studies included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

Quality and applicability of the included study

Green et al. 2013 was deemed only partially applicable to the guideline. This was primarily because it considered the US health care system, which differs substantially from the UK system. Wong et al. 2013 was also deemed to be only partially applicable despite being based in the UK. This was because of uncertainty over the applicability of some model inputs (QoL values and discount rates), details of which were omitted in the report.

Potentially serious limitations were identified in the study by Green et al. 2013. There was uncertainty over the treatment effect that had been applied in the model and there were concerns about the conclusions that had been drawn by the authors when interpreting the cost-effectiveness results. Very serious limitations were identified in the study by Wong et al. 2013. Omissions in the study report make it difficult to assess the quality of many of the input parameters used in the model e.g. the value and source of unit costs and resource use in the model are not fully reported.

Table 70: table showing methodological quality and applicability of the included studies.

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		
Potentially serious limitations		Green et al. 2013
Very serious limitations		Wong et al. 2013

Modified GRADE table

The primary results of the analyses by Green et al. 2013 and Wong et al. 2013 are summarised in the modified GRADE table below.

Table 71: modified grade table showing the included evidence (Green et al. 2013 and Wong et al. 2013) for the treatment of recurrent bladder cancer and previous low risk bladder cancer with and without histological sampling

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Green et al. 2013	Hypothetical cohort of patients with low-risk NMIBC after the initial transurethral resection of bladder tumour (TURBT).	**Full results**						**A series of one-way and two-way sensitivity analyses were conducted.** PIC + fulguration and fulguration alone were cost-effective in most analyses. PIC + fulguration and fulguration alone were co-dominant until annual recurrence increased to ≥14.2%, at which point fulguration alone was singularly dominant. PIC + fulguration became more cost-efficient than fulguration alone when total PIC costs moved towards zero. Strategies involving TURBT only cost-effective when the cost of TUBRT < $1175. Probabilistic sensitivity analysis (PSA) was not conducted.	Partially applicable as it considered the US health care system, which differs substantially from the UK system. Some potentially serious limitations were identified, including uncertainty over the treatment effect and an unusual interpretation of the cost-effectiveness results.
		No perioperative intravesical chemotherapy (PIC) + fulguration	$9,404.61	14.36	-	-	-		
		PIC + fulguration	$9,972.95	14.50	$568.34	0.14	$4,169.24		
		No PIC + TURBT	$10,641.23	14.34	$668.28	-0.16	Dominated		
		PIC + TURBT	$10,907.36	14.48	$934.41	-0.02	Dominated		

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
	Comments: Interventions are listed in dominance rank format.								
Wong et al. 2013	Patients with NMIBC that are elderly and frail or have multiple co-morbidities.	Inpatient cystodiathermy (IC)	£5,744.33	3.56 QALYs	Reference			One-way sensitivity analysis was conducted on the time horizon modelled. OLA was found to remain dominant when a 5 year time horizon or lifetime horizon was adopted. A further analysis considered the addition of PDD to OLA. OLA plus PDD was found to be dominant in comparison to IC. PSA was conducted. At a threshold of £30,000 per QALY, OLA was more cost-effective than IC in 81.49% or 84.1% of simulations (two values reported in study). With the addition of PDD to OLA, the strategy was more cost-effective than IC in 79.2% of simulations.	Partially applicable because of uncertainty over the applicability of some model inputs (QoL values and discount rates), details of which were omitted in the report. In addition, the objective of the analysis is only partly applicable to our decision problem . Serious limitations were also identified with omissions in the study report making it difficult to assess the quality of many of the input parameters applied in the model.
		Outpatient (office based) local anaesthetic (OLA)	£3,217.96	3.68 QALYs	-£2,526	0.12	OLA is dominant (more effective and cheaper)		
	Comments: Numerous omissions in the reporting of the study make it difficult to fully appraise the applicability and quality of the economic evaluation								

Evidence statements

Green et al. 2013 concluded that fulguration without perioperative intravesical chemotherapy was the most cost-effective strategy for treating low-risk NMIBC. However, unusually, the authors based this conclusion upon individual cost-effectiveness calculations rather than the standard incremental calculations. When following the more standard cost-effectiveness methodology using incremental cost-effectiveness ratios (ICERs), the strategy of perioperative intravesical chemotherapy (PIC) plus fulguration would most likely be considered the most cost-effective strategy with an ICER of $4,169 per QALY.

Of particular relevance to the topic at hand, was the finding that fulguration was more cost-effective than TURBT when both were used alone or when both were used in combination with intravesical chemotherapy. In both instances fulguration was found to be more effective and cheaper than TURBT alone i.e. dominant. However, as the study is US based, these results may lack applicability to the UK healthcare system.

Wong et al. 2013 found that outpatient laser ablation was cost-effective in comparison to inpatient cystodiathermy for the treatment of NMIBC, especially in elderly patients. In the base case, outpatient laser ablation was found to be cheaper (cost reduction of $2,526) and more effective (0.12 QALYs) than inpatient cystodiathermy and is thus dominant. A further analysis showed that using PDD in addition to outpatient laser ablation was also cost-effective and indeed dominant in comparison to inpatient cystodiathermy.

Probabilistic sensitivity analysis showed that, at a threshold of £30,000 per QALY, outpatient laser ablation had approximately an 80%[5] probability of being cost-effective in comparison to intravesical chemotherapy. With the addition of PDD to OLA, the strategy was more cost-effective than IC in 79.2% of simulations.

However, while the study is of some interest, it does not directly address the decision problem at hand because TURBT is not used as a comparator. The study instead compares two alternatives to TURBT and thus the key aspect of our decision problem remains unanswered by this study.

While both of these studies are somewhat useful, their lack of direct applicability to the decision problem under consideration makes it difficult to draw firm conclusions. As such, the cost-effectiveness of perioperative intravesical chemotherapy remains, to a large extent, uncertain.

References

1. Green DA, Rink M, Cha EK, Xylinas E, Chughtai B, Scherr DS, Shariat SF, Lee RK. Cost-effective treatment of low-risk carcinoma not invading bladder muscle. *BJU Int* 111(3B):E78-E83 2013

2. Wong KA, Zisengwe G, Athanasiou T, O'Brien T, Thomas K. Outpatient laser ablation of non-muscle invasive bladder cancer: is it safe, tolerable and cost-effective? *BJU Int* 112(5):561-7 Epub 2013

Full evidence table

[5] Note that an approximate figure is used as two figures are presented for cost-effectiveness probability in the study (81.49% and 84.1%).

The full details of the studies included in the evidence review are presented in the evidence table below.

Table 72: full evidence table showing the included evidence (Green et al. 2013 and Wong et al. 2013) for the treatment of recurrent bladder cancer and previous low risk bladder cancer with and without histological sampling

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Green et al. **Year:** 2013 **Country:** United states	**Type of analysis:** Cost-effectiveness analysis using QALYs as effectiveness measure i.e. cost-utility analysis. **Model structure:** Markov state transition model **Cycle length:** 3 months **Time horizon:** 5 years (60 months) **Perspective:** US healthcare payer perspective (Medicare costs are used). **Source of base-line data:** The probability of moving from a disease-free to a disease-recurrent state was	**Base case (population):** Hypothetical cohort of patients with low-risk NMIBC after the initial TURBT. **Sample size:** Not stated. Cost-effectiveness results presented appear to be per patient. **Age:** Not reported. **Gender:** Not reported. **Subgroup analysis:** No subgroup analyses were performed.	Fulguration was compared against transurethral resection of bladder tumour (TURBT) ***with and without*** a single dose of perioperative intravesical chemotherapy (PIC): • PIC + TURBT • PIC + fulguration • No PIC + TURBT • No PIC + fulguration	**Effectiveness (QALYs):** PIC + TURBT PIC + fulguration No PIC + TURBT No PIC + fulguration **Total costs:** PIC + TURBT PIC + fulguration No PIC + TURBT No PIC + fulguration **ICER (cost per QALY):** Comparisons in ***'dominance rank'*** format No PIC + fulguration ***PIC + fulguration*** No PIC + TURBT PIC + TURBT **Uncertainty:** One-way and two-way sensitivity analyses were conducted, with	14.48 14.50 14.34 14.36 $10,907.36 $9,972.95 $10,641.23 $9,404.61 Reference ***$4,169.24*** -$4,100.97 -$46,422.60 **Narrative summary of**	**Funding:** Supported in part by the Frederick J and Theresa Dow Wallace Fund of the New York Community Trust. **Comments** No conflicts of interest were reported.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	based on a meta-analysis reported by Sylvester et al. Data were used to estimate a constant 3-month recurrence rate for patients treated with and without PIC (2.7%). Disease progression was not modelled, which the authors state was because progression rates in the modelled population are very low and there is no evidence to suggest that deferral of PIC would have any impact on disease progression. **Source of effectiveness data:** The key effectiveness data informing the model is that described above. i.e. the reduction in recurrences associated with each treatment option). These figures were not well reported with only the recurrence rate for patients treated with PIC reported in			results presented graphically (using individual cost-effectiveness ratios for each intervention). Results are described here. **One-way sensitivity analyses** Efficacy of PIC on the annual recurrence rate of NMIBC was varied from 4% to 20%:	**sensitivity analysis results:** PIC + fulguration and fulguration alone were co-dominant until annual recurrence increased to ≥14.2%, at which point fulguration alone is singularly dominant. In addition, when annual recurrence was <10% PIC + TURBT showed a greater cost-efficiency than TURBT alone. PIC+TURBT was found to be more cost-efficient than TURBT alone when total PIC	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	the main text body. From a diagram in the report it appears that the following three monthly recurrence probabilities were applied for patients treated with and without PIC: Without PIC: 3.56% With PIC: 2.69% **Source of utility data:** Utility data for bladder cancer were obtained from similar, previously published analyses. From an input table in the report it appears that three utility weights were applied in the model: TURBT (-0.1) Cystoscopy (0.997) Fulguration (-0.05) **Source of cost data:** Direct procedural costs were derived from the Medicare			Total PIC cost (drug and delivery) was varied from $50 to $1000: Total TURBT cost was varied from $500 to $5000: **Two-way sensitivity analyses** Two sets of two-way sensitivity analyses were performed. One in which the efficacy of PIC and the cost of TURBT were varied simultaneously and another in which the cost of PIC and the cost of TURBT were varied	cost < $263. PIC + fulguration only became more cost-efficient than fulguration alone when total PIC costs moved towards zero. From a cost-effectiveness standpoint, TURBT was shown to become competitive with fulguration strategies when the cost of TURBT fell below $1175. Strategies involving TURBT were cost-effective only when TUBRT < $1175. PIC + fulguration and fulguration alone	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Resource Based Relative Value Scale, which functions as a standard for other fee schedules in the USA. The costs incorporated include the costs of surveillance, office based treatment, TURBT without PIC and TURBT with PIC. **Currency unit:** US dollars ($) **Cost year:** Not reported. **Discounting:** No discount rate is reported in the main text. However, from reading off a model diagram, it appears that a discount rate of 2.51% may have been applied.			simultaneously: **Probabilistic sensitivity analysis (PSA)** PSA was not conducted.	were similarly cost-effective when TURBT > $1175. Neither the efficacy of PIC nor it's cost had a significant impact on cost-effectiveness in comparison to the cost of TURBT.	
Study 2						
Author: Wong et al.	**Type of analysis:** Prospective cohort study and	**Base case (population):**	A. Outpatient (office based) local	**Effectiveness (QALYs):** OLA	3.68 [SD 0.52]	**Funding:** None stated.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Year: 2013 **Country:** UK	cost-effectiveness analysis. QALYs were used as the effectiveness measure i.e. cost-utility analysis. **Model structure:** Markov simulation model **Cycle length:** 1 year **Time horizon:** 10 years **Perspective:** UK NHS perspective **Source of base-line data:** Annual age and gender specific mortality rates were obtained from the UK Government Actuarial Department life tables. Bladder cancer-related mortality for NMIBC patients Peri-operative mortality rates were assumed to be similar to those of patients with similar	Patients with NMIBC that are elderly and frail or have multiple comorbidities. Exclusion criteria: • First presentation of tumour • Young age (< 50 years) • Large tumours (> 3cm) • Tumours adjacent to bladder neck • MIBC where patient is fit for curative intent • Presence of untreated urinary infection **Sample size:** 1000 patients **Age:** Mean patient age in trial was 77 years (range: 52-95).	anaesthetic (OLA) B. Inpatient cystodiathermy (IC) The addition of photodynamic diagnosis (PDD) was also considered in both treatment arms.	IC Incremental **Total costs:** OLA IC Incremental **ICER (cost per QALY):** **Uncertainty:** **One-way sensitivity analyses** One-way sensitivity analysis was conducted: **5 year time horizon** *Incremental QALYs* *Incremental costs* ICER **Lifetime horizon** *Incremental QALYs* *Incremental costs:*	3.56 [SD 0.50] 0.12 £3,217.96 [SD £359.17] £5,744.33 [SD £6,760.76] -£2,526.37 OLA dominant (more effective and less costly) 0.067 [SD 0.026] -£2,031.67 [SD £5,357.85] OLA dominant 0.147 [SD 0.059] -£2,576.42 [SD £7,293.07]	**Comments** No conflicts of interest were declared.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	demographic characteristics undergoing other minor operations under general anaesthetic. **Source of effectiveness data:** The data collected in the prospective trial part of the study was used to inform the economic model. This appears to be primarily the recurrence rates in each treatment arm. **Source of utility data:** Authors state that QALYs were generated for each intervention using survival and health-related QoL data. However, no detail is given on the QoL data that was used. **Source of cost data:** Procedural costs of OLA and IC were calculated using manufacturer-supplied costs of equipment and data from	**Gender:** Male : female ratio in trial was 1.39:1.00. **Subgroup analysis:** Not conducted.		ICER **PDD+OLA** *Incremental QALYs* *Incremental costs:* ICER **Probabilistic sensitivity analysis (PSA)** PSA was conducted to quantify the combined uncertainty associated with all model variables on the results. Results are presented using a cost-effectiveness plane scatter plot and cost-effectiveness acceptability curve (CEAC) and results are briefly described in the text. However, there are discrepancies between the figures and the text. ***Result from figure:*** At a threshold of £30,000 per QALY, OLA was more cost-effective than IC in 84.1% of the	OLA dominant 0.124 [SD 0.050] -£1961.56 [SD £6795.17] OLA dominant	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	the author's institution. It is unclear whether costs other than procedural costs were included in the model as no further detail is given on costs applied in the model. **Currency unit:** UK pound sterling (£) **Cost year:** Not reported. **Discounting:** Not reported.			simulations. ***Result quoted in text:*** At a threshold of £30,000 per QALY, there was an 81.9% probability that OLA was cost-effective. With the addition of PDD to OLA, it was still more cost-effective than IC with a certainty of 79.2%.		

3.3 Re-resection in high risk non-muscle invasive bladder cancer

Review question: Does re-resection in high risk NMIBC influence outcomes?

Rationale

High-grade non-muscle invasive (HGNMI) bladder cancer is an aggressive disease. The natural history of these cancers can be difficult to predict. Around 1 in 4 will progress to invade the bladder wall and may eventually spread beyond the bladder. Radical treatment, by either bladder removal (cystectomy) or radiotherapy, is necessary for tumours invading the bladder wall if cure is to be obtained. Whilst all patients with HGNMI bladder cancer are followed closely after initial treatment, a proportion of tumours progress to invasion and spread without detection. The risk of progression to invasion, or recurrence of another HGNMI cancer within the bladder, is related to several factors. These include pathological features of the tumour, patient factors and the practice of endoscopic transurethral resection. Whilst most surgeons agree on the need for an initial tumour resection, there is controversy regarding the role of an early, planned re-resection. This normally occurs within 6 weeks of the initial transurethral resection. It should reassess the site of the initial cancer and sample the urothelium within the bladder/prostatic fossa.

Advocates of re-resection report that a proportion of HGNMI tumours are found to actually be invasive upon re-assessment, and that pathological features missed in the initial resection may be detected. Furthermore, residual disease at re-resection is known to be a poor prognostic feature for the patient and may alter treatment plans. However, in many patients re-resection does not influence their treatment and adds cost to the healthcare provider and the risks of further surgery to the patient. Furthermore, some surgeons feel that the emphasis should be on an initial high-quality resection, so that all pathological factors and all invasive tumours are identified at this time. They argue that the re-resection delays the time to reaching a final pathological diagnosis.

This review will assess the evidence for re-resection in HGNMI bladder cancer and identify in which patients and tumours it is beneficial. It will identify measures of high quality re-resection that should be achieved by this procedure.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with newly confirmed high risk NMIBC following first TUR	Re -resection	No –re-resection	• Recurrence • Progression • Disease-specific survival • Radical treatment • Change/accuracy of staging • Residual tumour rate • Process-related morbidity • Health-related quality of life inc. Patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (NB) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. A second sift of the literature was conducted by another reviewer (JH) and any disagreement between reviewers was discussed. Data from randomised trials and one systematic review of observational studies was identified.

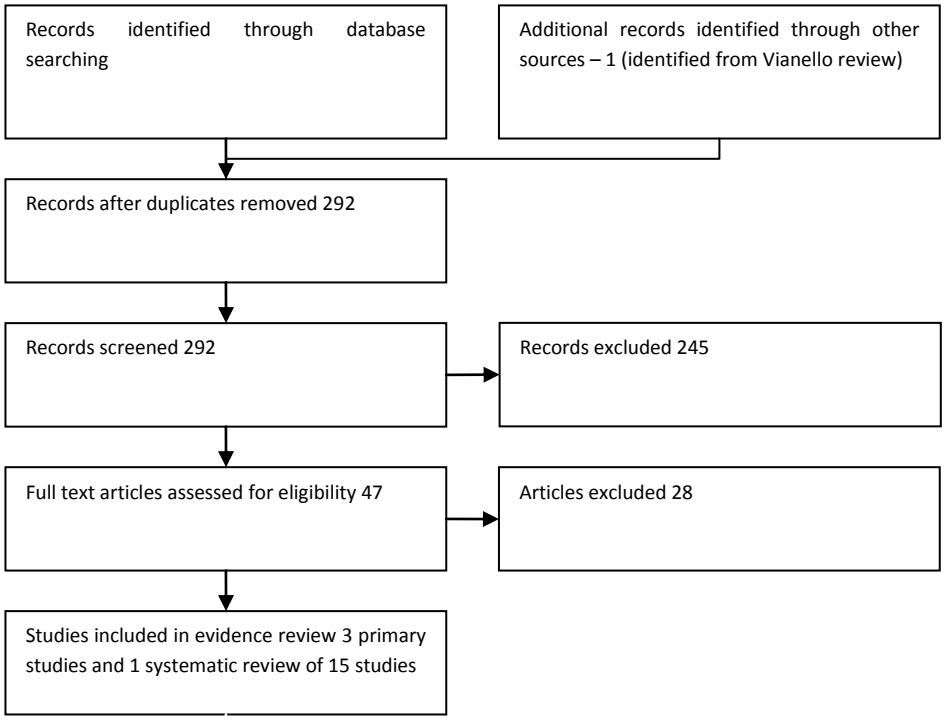
Data synthesis

Evidence was synthesised using RevMan and pooled effect sizes are reported in a GRADE evidence profile (Table 73) and forest plots (see Figures 52-53).

RESULTS

Result of the literature searches

Figure 51. Study flow diagram



Study quality and results

Low quality evidence was identified. The quality and results are summarised with GRADE in Table 73.

Evidence statements

Low quality evidence (Divrik *et al.*, 2010; Kim *et al.*, 2012) suggests a benefit for repeat transurethral resection in patients with high risk non muscle invasive bladder cancer in terms of bladder cancer recurrence, disease progression and bladder cancer specific mortality.

Using event free survival rates from the no re-resection group in Divrik *et al.* (2010) trial combined with the hazard ratios reported in Table 73 we could expect five year recurrence free survival rates of 63% following re-resection versus 33% without no re-resection. Estimated five-year progression-free survival would be 92% following re-resection group versus 76% without re-resection.

Low quality evidence (Divrik *et al.*, 2010) suggests re-resection is associated with minor complications in approximately 9% of cases, including prolonged bleeding, epididymitis and transient urinary retention. Such complications could be avoided in patients who do not undergo re-resection

A systematic review of observational studies (Vianello *et al.*, 2011) provided evidence of upstaging and tumour persistence rates at re-resection. For patients with stage T1 tumours at initial TURB, approximately 32% were found to have persistent tumour of the same or lower stage at repeated TURB. Around 9% of patients with T1 tumours at initial TURB were upstaged at repeat TURB.

No evidence was found about the impact of re-resection on health related quality of life in this population.

Table 73. GRADE Profile for re-resection versus no re-resection in people with high risk NMIBC

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Repeated resection	No repeated resection	Relative (95% CI)	Absolute	
Tumour recurrence (Divrik et al., 2010; Kim et al., 2012)											
2	randomised trials	serious[1]	none	none [2]	serious[3]	none	45/140 (32.1%)	93/148 (62.8%)	HR 0.41 (0.29 to 0.59)	5yr recurrence free survival 63% (52% to 73%) with repeated resection – versus 33% with no repeated resection[4]	⊕⊕OO LOW
Disease progression (Divrik et al., 2010)											
1	randomised trials	serious[1]	none	none	serious[3]	none	6/93 (6.5%)	23/98 (23.5%)	HR 0.29 (0.14 to 0.61)	5yr progression free survival 92% (85% to 96%) with repeated resection – versus 76% with no repeated resection[4]	⊕⊕OO LOW
Death from bladder cancer (Divrik et al., 2010)											
1	randomised trials	serious[1]	none	none	serious[3]	none	5/93 (5.4%)	11/98 (11.2%)	HR 0.35 (0.13 to 0.94)	Cannot calculate	⊕⊕OO LOW
Radical treatment rate (Divrik et al., 2010; Kim et al., 2012)											
2	randomised trials	serious[1]	none	none [2]	serious[3]	none	26/160 (16.3%)	36/161 (22.4%)	RR 0.73 (0.42 to 1.15)	67 fewer per 1000 (from 130 fewer to 34 more)	⊕⊕OO LOW
Process related morbidity of repeated TURB (minor complications) (Divrik et al., 2010)											
1	randomised trials	serious[1]	none	none	serious[3]	none	8/93 (8.6%)	0/98 (0%)	RR 17.9 (1.05 to 305.88)	86 more per 1000	⊕⊕OO LOW
Residual tumour rate in those with stage T1 tumours (presence of same or lower stage urothelial bladder cancer at repeated TURB)											
15	observational studies	none	none	none	none	none	454/1432 (31.7%)	-	-	317 per 1000	⊕⊕OO LOW
Upstaging rate in those with stage T1 tumours (presence of higher stage urothelial bladder cancer at repeated TURB)											
13	observational studies	none	none	none	none	none	74/833 (8.9%)	-	-	89 per 1000	⊕⊕OO LOW
T0 (disease free) rate at repeated TURB for those with stage T1 tumours at initial TURB											
15	observational studies	none	none	none	none	none	719/1432 (50.2%)	-	-	502 per 1000	⊕⊕OO LOW
Ta rate at repeated TURB for those with stage T1 tumours at initial TURB											
15	observational studies	none	none	none	none	none	132/1432 (9.2%)	-	-	92 per 1000	⊕⊕OO LOW
Tis rate at repeated TURB for those with stage T1 tumours at initial TURB											
15	observational studies	none	none	none	none	none	185/1432 (12.9%)	-	-	129 per 1000	⊕⊕OO LOW
Health related quality of life (including patient reported) - not measured											
0	No evidence										

[1] In Kim (2012) the initial TUR differed between treatment groups. In both studies (Divrik 2010, Kim 2012) analysis was not by intention to treat; [2] In Kim (2012) it was unclear whether all patients had high risk NMIBC - 50% had stage Ta tumours; [3] Low number of events (<300 in total); [4] Calculated using the pooled HR and the 5 year event free rates from the control arm of Divrik (2010)

Figure 52: Recurrence free survival forest plot

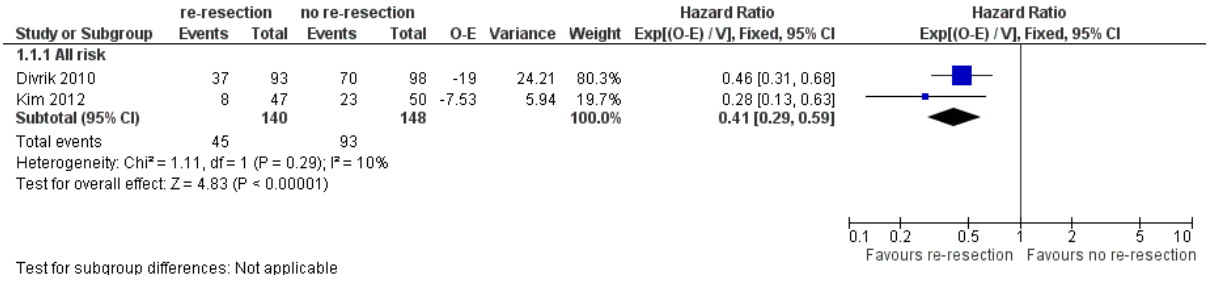
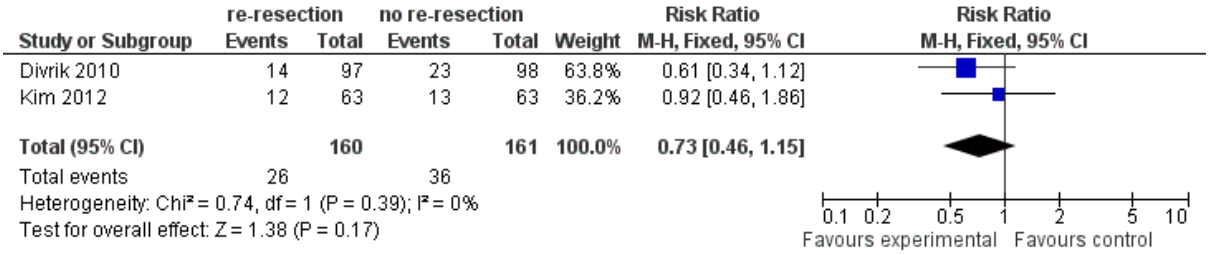


Figure 53: Cystectomy rate forest plot



References to included studies

Divrik, RT et al. Impact of routine second transurethral resection on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma with respect to recurrence, progression rate, and disease-specific survival: a prospective randomised clinical trial. European Urology 2010; 58(2): 185-190.

Kim, W et al. Value of immediate second resection of the tumor bed to improve the effectiveness of transurethral resection of bladder tumor. Journal of Endourology 2012; 26: 1059-1064.

Skolarus, TA et al. Use of restaging bladder tumor resection for bladder cancer among Medicare beneficiaries. Urology 2011; 78: 1345-1349.

Vianello, A et al. Repeated white light transurethral resection of the bladder in nonmuscle-invasive urothelial bladder cancers: systematic review and meta-analysis. Journal of Endourology 2011; 25: 1703-1712.

References to excluded studies (with reasons for exclusion)

Divrik, R. T., Sahin, A. F., & Ergor, G. (2010). Reply from authors re: Marko Babjuk. Second resection for non-muscle-invasive bladder carcinoma: current role and future perspectives. Eur Urol 2010;58:191-2 and Giacomo Novara, Vincenzo Ficarra. Does routine second transurethral resection affect the long-term outcome of patients with T1 bladder cancer? Why a flawed randomized controlled trial cannot address the issue. Eur Urol 2010;58:193-4. European Urology, 58, 195-196.

Reason: Authors reply to comment

Divrik, R. T., Yildirim, U., Zorlu, F., & Ozen, H. (2007). Re: The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: A prospective, randomized clinical trial. European Urology, 51, 1753.

Reason: Comment on the Divrik et al trial

Angbein, S., Guzman, S., Haecker, A., Weib, C., Michel, M. S., Alken, P. et al. (2006). [The influence of "differentiated trandurethral resection" in the recurrence and progression of superficial bladder cancer]. [Spanish]. Archivos Espanoles de Urologia, 59, 25-30.

Reason: Spanish language – is differentiated resection the same as repeated resection?

Aning, J. J. (2011). Early re-resection for T1 transitional cell carcinoma of the bladder-A study of current practice in the South West of England. British Journal of Medical and Surgical Urology, 4, 18-23.

Reason: Non comparative, possibly relevant to update Vianello review

Jahnson, S., Wiklund, F., Duchek, M., Mestad, O., Rintala, E., Hellsten, S. et al. (2005). Results of second-look resection after primary resection of T1 tumour of the urinary bladder. Scandinavian Journal of Urology & Nephrology, 39, 206-210.

Reason: All patients had early second-look resection – non comparative study.

Katumalla, F. S., Devasia, A., Kumar, R., Kumar, S., Chacko, N., & Kekre, N. (2011). Second transurethral resection in T1G3 bladder tumors - Selectively avoidable? Indian Journal of Urology, 27, 176-179.

Reason: Only patients with second TUR are reported – non comparative study.

Klan, R., Loy, V., & Huland, H. (1991). Residual tumor discovered in routine second transurethral resection in patients with stage T1 transitional cell carcinoma of the bladder. Journal of Urology, 146, 316-318.

Reason: Non – comparative, results are not reported for the 23 patients who did not have repeat TUR.

Kohrmann, K. U., Woeste, M., Kappes, J., Rassweiler, J., & Alken, P. (1994). The Value of Secondary Transurethral Resection for Superficial Bladder-Tumors. Aktuelle Urologie, 25, 208-213.

Reason: German language non comparative

Langbein, S., Badawi, K., Haecker, A., Weiss, C., Hatzinger, M., Alken, P. et al. (2006). Persistence, recurrence, and progression rates of superficial bladder tumours after resection using the differentiated technique. Medical Principles & Practice, 15, 215-218.

Reason: All patients had second resection – the comparison was between differentiated and non-differentiated technique.

Lopatkin, N. A., Martov, A. G., Gushchin, B. L., Gnatiuk, A. P., Ergakov, D. V., & Serebrianyi, S. A. (2003). [Diagnosis and treatment of recurrent surface cancer of the urinary bladder (early repeated cystoscopy and biopsy)]. [Russian]. Urologiia (Moscow, Russia), 45-49.

Reason: Russian language

Ojea, C. A., Nunez, L. A., Alonso, R. A., Rodriguez, I. B., Benavente, D. J., Barros Rodriguez, J. M. et al. (2001). [Value of a second transurethral resection in the assessment and treatment of patients with bladder tumor]. [Spanish]. Actas Urologicas Espanolas, 25, 182-186.

Reason: Spanish language non comparative

Orsola, A., Cecchini, L., Raventos, C. X., Trilla, E., Planas, J., Landolfi, S. et al. (2010). Risk factors for positive findings in patients with high-grade T1 bladder cancer treated with transurethral resection of bladder tumour (TUR) and bacille Calmette-Guerin therapy and the decision for a repeat TUR. BJU International, 105, 202-207.

Reason: Repeat TUR done in all T1b or greater cases – no matched comparison group, possibly relevant to update Vianello review

Parkin, J. (2011). G3T1 bladder cancer: Is early re-resection necessary? British Journal of Medical and Surgical Urology, 4, 13-17.

Reason: Non-comparative study, possibly relevant to update Vianello review

Richterstetter, M., Wullich, B., Amann, K., Haeberle, L., Engehausen, D. G., Goebell, P. J. et al. (2012). The value of extended transurethral resection of bladder tumour (TURBT) in the treatment of bladder cancer. BJU International, 110, E76-E79.

Reason: Non-comparative study, possibly relevant to update Vianello review

Rigaud, J., Karam, G., Braud, G., Glemain, P., Buzelin, J. M., & Bouchot, O. (2002). [T1 bladder tumors: value of a second endoscopic resection]. [French]. Progres En Urologie, 12, 27-30.

Reason: All patients had early second TUR – non comparative study.

Rodriguez-Rubio Cortadellas, F. I., Garrido, I. S., Rivas, A. D., Hens, P. A., Bachiller, B. J., Beltran, A., V et al. (2001). [Second resection in patients with Ta-T1 bladder tumors]. [Spanish]. Actas Urologicas Espanolas, 25, 553-558.

Reason: Spanish language non comparative

Schulze, M., Stotz, N., & Rassweiler, J. (2007). Retrospective analysis of transurethral resection, second-look resection, and long-term chemo-metaphylaxis for superficial bladder cancer: indications and efficacy of a differentiated approach. Journal of Endourology, 21, 1533-1541.

Reason: Repeat TUR done in all high risk cases – no matched comparison group

Shen, H.-B. (2012). Clinical analysis of re-transurethral resection in management of non-muscle invasive bladder urothelial cancer. Journal of Shanghai Jiaotong University (Medical Science), 32, 491-494.

Reason: Chinese language – no mention of randomization

Shen, Y. J., Ye, D. W., Yao, X. D., Zhang, S. L., Dai, B., Zhu, Y. P. et al. (2009). [Repeat transurethral resection for non-muscle invasive bladder cancer]. [Chinese]. Chung-Hua Wai Ko Tsa Chih [Chinese Journal of Surgery], 47, 725-727.

Reason: Exclude – Chinese language, non comparative.

Vasdev, N. (2011). The role of early re-resection in pTaG3 transitional cell carcinoma of the urinary bladder. British Journal of Medical and Surgical Urology, 4, 158-165.

Reason: Non randomized study – historical comparison group.

Vogeli, T. A., Grimm, M. O., Simon, X., & Ackermann, R. (2002). [Prospective study of effectiveness. Reoperation (re-TUR) in superficial bladder carcinoma]. [German]. Urologe (Ausg, A). 41, 470-474.

Reason: German language non comparative

Wilby, D. (2009). Comparison of re-resection rates for new G3pT1 bladder cancer, in patients randomised to initial blue light or white light resection: 1 year follow up data. Journal of Endourology, Conference, A67.

Reason: Abstract only – compares blue with white light resection,

Wong, S. S. W. (2009). Pathological staging of superficial high-grade bladder transitional cell carcinoma at re-resection. Journal of Urology, Conference, var-640.

Reason: Abstract only – non comparative all had re-resection.

Yucel, M., Hatipoglu, N. K., Atakanli, C., Yalcinkaya, S., Dedekarginoglu, G., Saracoglu, U. et al. (2010). Is repeat transurethral resection effective and necessary in patients with T1 bladder carcinoma? Urologia Internationalis, 85, 276-280.

Reason: All patients had early second TUR – non comparative study, possibly relevant to update Vianello review

Holmang, S. High-grade non-muscle-invasive bladder cancer: is re-resection necessary in all patients before intravesical bacillus Calmette-Guerin treatment? Scandinavian Journal of Urology 2013; 47(5): 363-369

Reason: Non randomized study

Sfakianos, JP et al. The effect of restaging transurethral resection on recurrence and progression rates in patients with nonmuscle invasive bladder cancer treated with intravesical bacillus Calmette-Guerin. Journal of Urology 2014; 191(2): 341-345.

Reason: Non randomized study

Suer, E et al. Time between first and second transurethral resection of bladder tumors in patients with high-grade T1 tumors: is it a risk factor for residual tumor detection? Urologia Internationalis 2013; 91(2): 182-186.

Reason: Non-comparative study, possibly relevant to update Vianello review

Lazica, DA et al. Second transurethral resection after ta high-grade bladder tumor: a 4.5-year period at a single university center. Urologia Internationalis 2014; 92(2): 131-135.

Reason: Non-comparative study, possibly relevant to update Vianello review

Evidence tables

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Divrik 2010
Turkey</td>
<td>Randomised clinical trial
2001-2005</td>
<td>210</td>
<td>Inclusion criteria: newly diagnosed pT1 bladder cancer. Patients receiving BCG or radical cystectomy following second TURB (n=12) or lost to follow up (n=7) were excluded from the analysis.
<table>
<tr><th rowspan="2">Group</th><th colspan="2">Grade</th></tr>
<tr><th>Low</th><th>High</th></tr>
<tr><td>Repeat TURB</td><td>48 (52%)</td><td>45 (48%)</td></tr>
<tr><td>No repeat</td><td>54 (55%)</td><td>44 (45%)</td></tr>
</table>
<table>
<tr><th rowspan="2">Group</th><th colspan="2">Multiple tumours or tumours >3cm</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Repeat TURB</td><td>73 (78%)</td><td>20 (12%)</td></tr>
<tr><td>No repeat</td><td>82 (84%)</td><td>16 (16%)</td></tr>
</table>
</td>
<td>Second TURB done for any residual tumour or scar of the first resection within 2-6 weeks of the first resection.</td>
<td>No second TURB for residual tumour or scar of the first resection.</td>
<td>Mean follow-up was 66 months for both groups</td>
<td>Tumour recurrence (2nd TURB vs no 2nd TURB)
37/93 vs 70/98, (P<0.0001, log rank test)
In subgroup analysis of those with low grade tumours or single tumours , recurrence rate was not statistically significant between the treatment arms (P=0.055 and P=0.070 respectively).
Progression (2nd TURB vs no 2nd TURB)
7/93 vs 24/98, (P<0.0001, log rank test)
Overall mortality (2nd TURB vs no 2nd TURB)
30/93 vs 35/98, (P=0.363, log rank test)
Cancer specific mortality (2nd TURB vs no 2nd TURB)
5/93 vs 11/98, (P=0.038, log rank test)
Cystectomy after TUR (2nd TURB vs no 2nd TURB)
14/97 versus 23/98 (P=0.031)</td>
<td>Authors disclosed no conflicts of interest.</td>
<td>No intention to treat analysis – BCG or radical cystectomy excluded from analysis</td>
</tr>
<tr>
<td>Kim 2012

Korea</td>
<td>Randomised clinical trial</td>
<td>126</td>
<td>Inclusion criteria: major axis of tumour > 2cm, 2 or more tumours, patients had previous intermediate or high risk tumours, the tumours were non-papillary and the tumours had a broad based shape

Patients who underwent cystectomy (19 T2</td>
<td>Second TURB done immediately after first TURB was grossly complete.

TURB was</td>
<td>Initial TURB only – stopped when grossly complete.

65% had MP in</td>
<td>Mean follow-up was 16 months for the repeat TURB group and</td>
<td>Tumour recurrence (2nd TURB vs no 2nd TURB)

8/47 vs 23/50; HR=0.274 (95%C.I. 0.112 to 0.669)

For high risk group (T1 or TaG3)</td>
<td>No competing financial interests declared</td>
<td>No intention to treat analysis – 19 T2 and 6 T1G3 excluded</td>
</tr>
</table>

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>and 6 T1G3) were excluded from the analysis.

<table><tr><th rowspan="2">Group</th><th colspan="4">Tumour stage</th></tr><tr><th>Ta</th><th>T1</th><th>T2</th><th>CIS</th></tr><tr><td>Repeat TURB</td><td>32</td><td>17</td><td>12</td><td>2</td></tr><tr><td>No repeat</td><td>32</td><td>18</td><td>12</td><td>1</td></tr></table>
<table><tr><th rowspan="2">Group</th><th colspan="2">Grade</th></tr><tr><th>Low</th><th>High</th></tr><tr><td>Repeat TURB</td><td>25</td><td>38</td></tr><tr><td>No repeat</td><td>31</td><td>32</td></tr></table></td><td>repeated until MP in specimen was confirmed by intra-TUR frozen biopsy results..</td><td>TURB specimen</td><td>17 months for the non-repeat group.</td><td>2yr recurrence rates were 27.5% versus 58% (P=0.015, log rank test)

For low risk group 2yr recurrence rates were 50.1% versus 52.6% (P=0.015, log rank test)

Cystectomy within 3 months after TUR (2nd TURB vs no 2nd TURB)

12/63 versus 13/63</td><td></td><td>from analysis due to cystectomy.

Sub optimal first TURB in the comparison group?

Unclear whether all were high risk NMIBC</td></tr>
<tr><td>Skolarus 2011

USA</td><td>Observational study

1992-2005</td><td>62016</td><td>Patients with any stage bladder cancer, were identified from the SEER Medicare database (age 66 years or older).

<table><tr><th></th><th colspan="3">Restaging resection</th></tr><tr><th>Stage</th><th>No</th><th>Yes</th><th>Total</th></tr><tr><td>Ta</td><td>31840</td><td>913</td><td>32753</td></tr><tr><td>T1</td><td>11255</td><td>964</td><td>12219</td></tr></table></td><td>Restaging bladder tumour resection (2 or more TURB resections within 60 days of diagnosis)</td><td>No restaging resection</td><td>Between 1 and 14 years</td><td>Cancer specific survival – number of deaths not reported. Models adjusted for age, gender, race, socioeconomic status, tumour grade, intravesical therapy and major bladder cancer treatment interventions

Stage Ta

Unadjusted HR=1.54 (95% C.I. 1.21 to 1.97)</td><td>American Cancer Society, American Urological association, Astellas Pharma and NIH grant</td><td>Unclear whether initial TURB was grossly complete (repeat TURB might have been for incomplete initial TURB).</td></tr>
</table>

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td><table><tr><td>T2</td><td>8741</td><td>840</td><td>9581</td></tr><tr><td>T3/4</td><td>5052</td><td>312</td><td>5364</td></tr></table></td><td></td><td></td><td></td><td>Adjusted HR=1.24 (1.21 to 1.97)

Stage T1

Unadjusted HR=1.01 (0.85 to 1.21)

Adjusted HR=1.01 (0.84 to 1.21)

Stage T2

Unadjusted HR=0.81 (0.71 to 0.93)

Adjusted HR=0.77 (0.67 to 0.93)

Stage T3/T4

Unadjusted HR=0.78 (0.67 to 0.93)

Adjusted HR=0.85 (0.72 to 1.01)</td><td></td><td></td></tr>
<tr><td>Vianello 2011

Italy</td><td>Systematic review of observational studies</td><td>2464 (from 15 studies, 1998 to 2008), 2262 had repeated TURB</td><td>All were NMIBC

At first TURB:

<table><tr><th></th><th>G1</th><th>G2</th><th>G3</th><th>Gx</th><th>Total</th></tr><tr><td>Ta</td><td>173</td><td>106</td><td>349</td><td>188</td><td>816</td></tr><tr><td>T1</td><td>85</td><td>198</td><td>883</td><td>299</td><td>1432</td></tr><tr><td>Tis</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>14</td></tr></table>Gx – grade not assessed.</td><td>Repeated white light TURB, 2 to 8 weeks after initial TURB</td><td>N one</td><td>NA</td><td>Pooled prevalence of Ta tumour in repeated TURB was 0.39 (95% C.I. 0.26 to 0.54).

Pooled prevalence of T1 tumour in repeated TURB was 0.47 (95% C.I. 0.41 to 0.53).

For stage T1 tumours the rate of persistent tumour at repeat TURB was 454/1432 (32%, range 15% to 55%).

For stage T1 tumours the rate of upstaging at repeated TURB was</td><td>No competing financial interests declared</td><td></td></tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			Lesion sizes not reported.				**74/ 833 (9%, range 0% to 24%)**		

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3.3.1 BCG or primary cystectomy in high risk non-muscle invasive bladder cancer

Review question: For which patients with non-muscle invasive bladder cancer would primary cystectomy produce better outcomes than BCG?

Rationale

High-grade non-muscle invasive (HGNMI) bladder cancer is an aggressive disease. The natural history of these cancers is difficult to predict. Around 1 in 4 will eventually progress to invade the bladder wall and may spread beyond the bladder to cause death. Invasion marks a dramatic worsening in prognosis for the patient and needs aggressive treatment if cure is to be obtained. Whilst various pathological factors can be used to guide the risk of developing invasion from a HGNMI tumour, none offer absolute certainty to the patient.

Currently, many urologists offer an initial treatment of BCG immunotherapy for HGNMI bladder cancer. BCG may reduce the chance of a tumour progressing to invasion but has side effects and can delay the identification of worsening cancers. This delay may affect the cure rate for aggressive cancers. Advocates of BCG suggest this treatment may reduce progression rates for individual tumours, allows the identification of patients with non-progressing cancers (and so these patients do not receive radical treatment) and is safe if the bladder is monitored closely. In contrast, other physicians claim that BCG is not effective at reducing progressing and delays the identification of worsening disease such that it reduces the chances of cure in the patients. An alternate approach to BCG is primary radical treatment (usually cystectomy) for HGNMI cancers. This may be the safest option for patients, but will lead to over treatment for those whose cancers would not progress to invasion and carries the risks of major surgery or radiotherapy. Although radical radiotherapy / chemo-radiotherapy is used to treat muscle invasive bladder cancer, evidence to support its use in the HGNMI disease is less compelling. Various pathological and clinical factors may be used to guide the risk of progression and the treatment options.

This review will look at the evidence of BCG and primary radical treatment (cystectomy) for HGNMI bladder cancer. It will estimate the risks and benefits of each approach and try to identify factors that would be useful in aiding patient choice.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients diagnosed with high risk NMIBC with no prior BCG therapy Subgroups: - Male/female - Pathology features - Solitary tumour - Multifocal tumour - Extent of Lamina propria involvement - Presence of CIS	Primary Cystectomy Primary Radiotherapy/ chemoradiotherapy	BCG therapy	• Overall survival • Disease-specific survival • Metastasis free survival • Bladder preservation rates • Treatment related mortality • Treatment related morbidity • Health-related quality of life, inc patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

Randomised trials and comparative studies were included in the evidence review. After discussion with the GDG it was decided to also include the two largest series of patients (one cohort of patients treated with BCG and one treated with cystectomy) in order to benchmark the survival data from comparative studies. The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. Studies comparing primary treatments were included, as were studies comparing primary versus deferred cystectomy, in order to assess the clinical outcomes of undergoing initial bladder-sparing treatment.

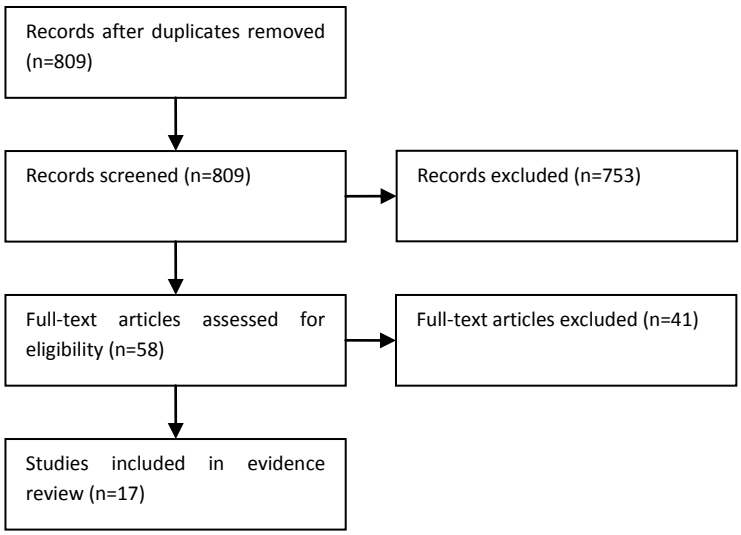
Data synthesis

Data from comparative studies were pooled using RevMan to provide overall effect estimates. The case series studies are summarised in Table 74-78.

RESULTS

Result of the literature searches

Figure 51. Study flow diagram



Study quality and results

The quality of the evidence was assessed using GRADE. The evidence is summarised in Tables 74-78 and Figures 52-53.

Evidence statements

Radiotherapy versus observation or BCG therapy

Moderate quality evidence from one randomised trial of 204 patients (Harland *et al.*, 2007) suggests uncertainty over whether radiotherapy is more or less effective than observation or BCG therapy in terms of recurrence-free survival, progression-free survival and overall survival. 5/102 (5%) of patients in the radiotherapy arm experienced long-term toxicity. 18% of the radiotherapy arm and 13% of the control arm underwent cystectomy due to recurrence or progression.

Primary cystectomy versus primary conservative treatment

Very low quality evidence from two retrospective studies suggests uncertainty over whether primary cystectomy is more or less effective than primary conservative treatment (observation or intravesical therapy) in terms of progression or overall survival. Conservative treatment was associated with better five-year disease-specific survival than primary cystectomy in three studies (Badalato *et al.*, 2012; Park *et al.*, 2009; Patard *et al.*, 2001). However, in one study (Park *et al.*, 2009) patients undergoing cystectomy were older, more likely to have proper muscle absent in the TUR specimen and included a higher proportion of gross non-papillary tumours, all of which were associated with reduced disease-specific survival. Three studies reported disease-specific mortality rates in 337 patients. There were no differences in disease-specific mortality in two studies. Low quality evidence from six studies reported a subsequent cystectomy rate of 26% in patients initially treated by conservative therapy.

Early cystectomy versus deferred cystectomy

Very low quality evidence from one study suggests uncertainty of a difference in five-year overall survival between patients treated with early cystectomy compared with patients undergoing deferred cystectomy after BCG failure (72.2% versus 73.2% five-year survival, p=0.75). Three studies suggest reduced disease-specific survival in patients undergoing deferred cystectomy, with five-year disease-specific survival ranging from 78% to 84% across studies for early cystectomy and from 67% to 75% across studies for deferred cystectomy. Ten-year disease-specific survival ranged from 69% to 79% across studies for early cystectomy and from 51% to 64% for deferred cystectomy. Denzinger *et al.* (2009) reported that concomitant CIS was related to a decrease in disease-specific survival in the deferred cystectomy group only. One systematic review reported that disease-specific survival after progression from high-risk NMIBC in initially conservatively treated patients was 35% after a median follow-up of 48-123 months (van den Bosch *et al.*, 2011). The disease-specific mortality rate in 1136 clinical T1G3 patients who underwent radical cystectomy was 29.8% at five years (Fritsche *et al.*, 2010). 50% of this cohort were upstaged to pT2 or higher at cystectomy.

One study reported that 7% of patients had major surgical complications which were distributed equally between early and deferred cystectomy groups, including two fatal pulmonary embolias and one fatal cardiac ishaemia.

One study (Kamat *et al.*, 2006) provides very low quality evidence from 30 patients with micro-papillary bladder cancer. 12 patients undergoing cystectomy as initial therapy had ten-year disease-specific survival of 72%, whilst in 18 patients who underwent cystectomy after progression the median disease-specific survival was 61.7 months with no patient surviving ten years. Very low quality evidence from one study (Cheng *et al.*, 1999) of patients with primary CIS suggests uncertainty about a difference in 15-year progression-free survival and disease-specific survival between those treated with immediate cystectomy and those that were not (some deferred

cystectomy, some intravesical therapy). Radical cystectomy performed within three months after the initial diagnosis was associated with improved overall survival, but this was not significant after controlling for age.

Table 74. GRADE evidence profile: Radiotherapy versus control (observation or intravesical therapy) for T1G3 bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	Control	Relative (95% CI)	Absolute	
Progression (time to detection of pT2 tumour or higher, cystectomy, metastases or treatment; follow-up median 44 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	32/102 (31.4%) Median interval not met	33/102 (32.4%) Median interval not met	HR 1.07 (0.65 to 1.74)	5-year progression-free interval 62% versus 63%	⊕⊕⊕O MODERATE
Progression (as above but death from any cause included as event; follow-up median 44 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	57/102 (55.9%) Median 49 months	49/102 (48%) Median 66 months	HR 1.35 (0.92 to 1.98)	5-year progression-free survival 41% versus 52%	⊕⊕⊕O MODERATE
Death from any cause (follow-up median 44 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	45/102 (44.1%) Median 67 months	39/102 (38.2%) Median 88.5 months	HR 1.32 (0.86 to 2.04)	5-year overall survival 52.5% versus 61%	⊕⊕⊕O MODERATE
Recurrence (time to recurrence of a bladder tumour (invasive or otherwise), cystectomy, metastases or treatment or disease-related death; follow-up median 44 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	61/102 (59.8%) Median 16 months	66/102 (64.7%) Median 12.5 months	HR 0.77 (0.54 to 1.10)	5-year recurrence-free interval 40% versus 30.5%	⊕⊕⊕O MODERATE
Recurrence (as above but death from any cause included as an event; follow-up median 44 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	78/102 (76.5%) Median 13 months	71/102 (69.6%) Median 12 months	HR 0.94 (0.67 to 1.30)	5-year recurrence-free survival 31% versus 29%	⊕⊕⊕O MODERATE
Long-term toxicity (assessed 12 months or more after study entry)											
1[1]	randomised trials	none	none	none	serious[2]	none	5/102 (4.9%)	0/102 (0%)	-	-	⊕⊕⊕O MODERATE
Cystectomy rate											
1[1]	randomised trials	none	none	none	serious[2]	none	18/102 (17.6%)	13/102 (12.7%)	RR 1.38 (0.72 to 2.67)	48 more per 1000 (from 36 fewer to 213 more)	⊕⊕⊕O MODERATE
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Harland 2007; [2] Low number of events / confidence interval includes value of no effect

Table 75. GRADE evidence profile: Primary cystectomy versus conservative treatment (surveillance or intravesical therapy) for high-risk non muscle invasive bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Primary RC	Conservative treatment	Relative (95% CI)	Absolute	
Progression (median follow-up 6.9 – 8.3 years; assessed with: Number of patients progressing over follow-up)											
2[1]	observational studies	none	none	none	serious[2]	none	27/101 (26.7%)	55/172 (32%)	RR 0.86 (0.58 to 1.27)	45 fewer per 1000 (from 134 fewer to 86 more)	⊕OOO VERY LOW
Overall mortality (median follow-up 6.9 – 8.3 years; assessed with: 10-yr overall mortality rate)											
2[1]	observational studies	none	none	none	serious[2]	none	71/164 (43.3%)	75/172 (43.6%)	RR 1.00 (0.78 to 1.28)	0 fewer per 1000 (from 96 fewer to 122 more)	⊕OOO VERY LOW
Overall mortality (median follow-up 4.3 – 6.9 years assessed with: 5-yr overall mortality rate)											
2[3]	observational studies	none	none	none	serious[2]	none	31/113 (27.4%)	82/425 (19.3%)	RR 1.38 (0.97 to 1.95)	73 more per 1000 (from 6 fewer to 183 more)	⊕OOO VERY LOW
Disease-specific mortality (median follow-up 62 mo – 8.3 years assessed with: mortality rate due to bladder cancer)											
3[4]	observational studies	none	none	none	serious[2]	none	29/115 (25.2%)	46/222 (20.7%)	RR 1.22 (0.81 to 1.84)	-	⊕OOO VERY LOW
Disease-specific survival at 5 years											
3[5]	observational studies	serious[6]	none	none	serious[2]	none	64% to 84%	80% to 96%	n/a	All 3 studies favour conservative treatment for 5yr DSS rates	⊕OOO VERY LOW
Cystectomy rate											
6[7]	observational studies	none	none	none	none	none	-	238/914 (26%)[8]	-	-	⊕⊕OO LOW
Treatment-related mortality											
0	No evidence										
Treatment-related morbidity											
0	No evidence										
Health-related quality of life											
0	No evidence										

[1] De Berardinis 2011, Thalman 2004; [2] Low number of events / confidence interval includes value of no effect; [3] Thalman 2004, Dalbagni 2009; [4] De Berardinis 2011, Thalman 2004, Patard 2001; [5] Badalato 2012, Park 2009, Thalman 2004; [6] In Park (2009) patients undergoing RC were older, more likely to have proper muscle absent in the TUR specimen and a higher proportion of gross non-papillary tumours, all of which were factors associated with reduced disease-specific survival. Inclusion of this study increases the effect size and confidence interval in favour of conservative treatment; [7] De Berardinis 2011, Thalman 2004, Patard 2001, Badalato 2012, Dalbagni 2009, Iida 2009; [8] None of the studies reported a significant difference in survival between primary RC and delayed RC

Table 76. GRADE evidence profile: Early cystectomy versus deferred cystectomy for high-risk non-muscle invasive bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Primary RC	Deferred RC	Relative (95% CI)	Absolute	
Metastases-free survival											
0	No evidence available										
Overall mortality (follow-up median 53 months; assessed with: 5-yr mortality rate)											
1[1]	observational studies	none	none	none	serious[2]	none	10/36 (27.8%)	11/41 (26.8%)	RR 1.04 (0.50 to 2.15)	11 more per 1000 (from 134 fewer to 309 more)	⊕OOO VERY LOW
Disease-specific mortality (follow-up median 58 mo to 5.4 yrs; assessed with: 5-yr mortality rate)											
3[3]	observational studies	none	none	none	serious[2]	none	67/363 (18.5%)	62/220 (28.2%)	RR 0.65 (0.48 to 0.89)	99 fewer per 1000 (from 31 fewer to 147 fewer)	⊕OOO VERY LOW
Disease-specific mortality (follow-up median 58 mo to 5.4 yrs; assessed with: 10-yr mortality rate)											
3[3]	observational studies	none	none	none	serious[2]	none	91/363 (25.1%)	85/220 (38.6%)	RR 0.65 (0.51 to 0.84)	135 fewer per 1000 (from 62 fewer to 189 fewer)	⊕OOO VERY LOW
Disease-specific mortality (Micropapillary tumours) (follow-up 1.7-181.2 months)											
1[4]	observational studies	none	none	none	serious[5]	none	2/12 (16.7%)	8/18 (44.4%)	RR 0.38 (0.10 to 1.47)	276 fewer per 1000 (from 400 fewer to 209 more)	⊕OOO VERY LOW
Disease-specific mortality (CIS only) (follow-up mean 11 years)											
1[6]	observational studies	none	none	serious[7]	serious[5]	none	10/43 (23.3%)	27/95 (28.4%)	RR 0.82 (0.44 to 1.54)	51 fewer per 1000 (from 159 fewer to 153 more)	⊕OOO VERY LOW
Overall mortality (CIS only) (follow-up mean 11 years)											
1[6]	observational studies	none	none	serious[7]	serious[5]	none	17/43 (39.5%)	66/95 (69.5%)	RR 0.57 (0.38 to 0.84)	299 fewer per 1000 (from 111 fewer to 431 fewer)	⊕OOO VERY LOW
Treatment-related mortality											
1[8]	observational studies	none	none	none	serious[9]	none	3/105 (2.9%)[10]		-	-	⊕OOO VERY LOW
Treatment-related morbidity (assessed with: impaired wound healing)											
1[8]	observational studies	none	none	none	serious[9]	none	4/105 (3.8%)		-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Wong, 2009 (abstract only); [2] Small sample size / low number of events;[3] Hautmann 2009, Denzinger 2008, Ali-el-Dein 2011, [4] Kamat 2006; [5] Low number of events / confidence interval includes null value; [6] Cheng, 1999; [7] Control group includes patients who underwent deferred RC and those treated with intravesical therapy or radiotherapy only; [8] Denzinger, 2008; [9] Low number of events - events not reported separately for early and deferred RC; [10] 2 fatal pulmonary embolia, 1 fatal cardiac ischaemia

Table 77. Disease-specific survival (DSS) in patients with high-risk NMIBC and progression after initial conservative treatment (reported in systematic review by van den Bosch, 2011)

Study type (n studies/patients)	Median follow-up	Progression to MIBC	Death from disease	DSS in case of progression
Prospective (7 studies/1183 patients)	Range 52-123 mo	258 (22%)	176 (15%)	32% (range 13-64)
Retrospective (12 studies/1905 patients)	Range 48-107 mo	401 (21%)	252 (13%)	37% (range 7-59)
Total (19 studies/3088 patients)	**Range 48-123 mo**	**659 (21%)**	**428 (14%)**	**35%**

Table 78. Recurrence, disease-specific mortality and overall mortality of 1136 T1G3 NMIBC patients treated with radical cystectomy and bilateral lymphadenectomy (Fritsche, 2011) (51% of patients were upstaged to pT2 or higher)

	Overall recurrence	Overall disease specific mortality	Overall mortality
2-year	22.5%	7.3%	8%
5-year	31.9%	29.8%	44%
8-year	34.5%	35.5%	53%

Figure 52. Primary cystectomy versus primary conservative therapy; Outcome, Disease-specific mortality rate

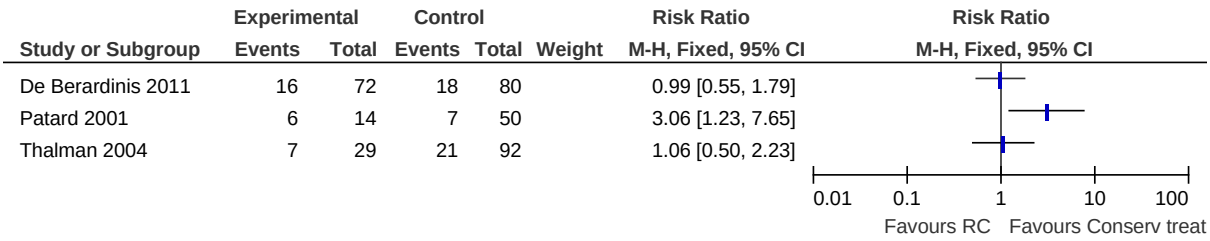
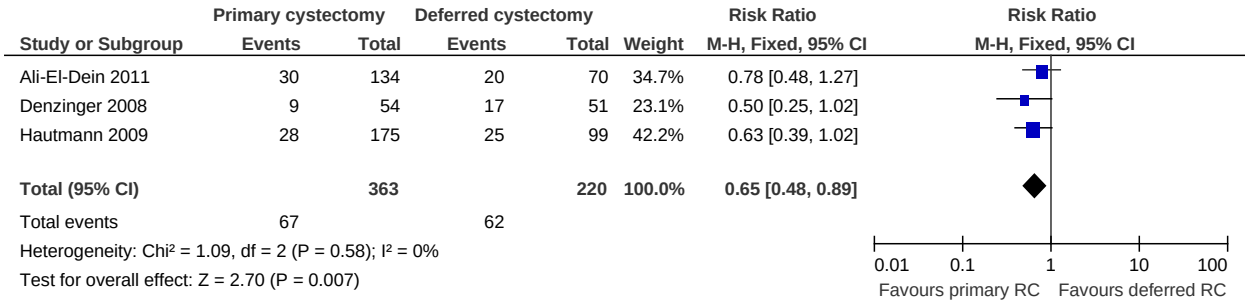


Figure 53. Early cystectomy versus deferred cystectomy; Outcome, 5-yr disease-specific mortality rate



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Fritsche, HM et al. Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. European Urology 2010; 57(2): 300-309.

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van den Bosch, S and Alfred, WJ. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. [Review]. European Urology 2011; 60(3): 493-500.

Wong, SW. Immediate versus delayed cystectomy for high-grade PT1 Transitional Cell Carcinoma of the bladder. BJU International Conference(var.pagings): 4

References to excluded studies (with reasons for exclusion)

Droller, MJ. Tumor progression and survival in patients with T1G3 bladder tumors: multicentric retrospective study comparing 94 patients treated during 17 years. Journal of Urology 2002; 168(2): 855-856.

Reason: Comment on Patard 2002

Sternberg, IA. The role of immediate radical cystectomy in the treatment of patients with residual T1 on restaging transurethral resection. Journal of Urology 2012; Conference(var.pagings): 4

Reason: Abstract only, unclear if relevant to PICO

Kulkarni, GS et al. Cost-effectiveness analysis of immediate radical cystectomy versus intravesical Bacillus Calmette-Guerin therapy for high-risk, high-grade (T1G3) bladder cancer (Structured abstract). Cancer 2009; 115: 5450-5459.

Reason: Health Economics

Kulkarni, GS et al. Optimal management of high-risk T1G3 bladder cancer: a decision analysis. PLoS Medicine / Public Library of Science 2007; 4(9): e284

Reason: Health Economics

Jager, W et al. Early vs delayed radical cystectomy for 'high-risk' carcinoma not invading bladder muscle: delay of cystectomy reduces cancer-specific survival. BJU International 2011; 108(8 Pt 2): E284-E288.

Reason: Comparison not relevant to PICO. Not reported if other primary treatment received before delayed cystectomy. Time to cystectomy as continuous variable.

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Reason: Comparison not relevant to PICO

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Reason: Not relevant to PICO. RC preceded by RT.

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Reason: Not relevant to PICO. No primary RC.

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Reason: Non-comparative

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Reason: Not relevant to PICO. Doesn't compare BCG and RC treated patients

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Reason: Comparison not relevant to PICO. Includes MIBC

Lambert, EH et al. The increasing use of intravesical therapies for stage T1 bladder cancer coincides with decreasing survival after cystectomy. BJU International 2007; 100(1): 33-36.

Reason: Non-comparative. All patients had RC, no primary IVT

Kulkarni, JN and Gupta, R. Recurrence and progression in stage T1G3 bladder tumour with intravesical bacille Calmette-Guerin (Danish 1331 strain). BJU International 2002; 90(6): 554-557.

Reason: Non-comparative

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Reason: Non-comparative

Villar, A et al. External beam irradiation for T1, T2-3 and T4 transitional cell carcinoma of the urinary bladder. Radiotherapy & Oncology 1987; 9(3): 209-215.

Reason: Non-comparative, unclear if high-risk NMIBC

Herr, HW and Sogani, PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? Journal of Urology 2001; 166(4): 1296-1299.

Reason: Not relevant to PICO. All previous BCG before RC

Zietman, AL. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: Management and consequences of TA, T1, and TIS recurrence within the retained bladder. Urology 2001; 58(3): 380-385.

Reason: Population not relevant (MIBC)

Shahin, O et al. A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guerin for primary stage T1 grade 3 bladder cancer: recurrence, progression and survival. Journal of Urology 2003; 169(1): 96-100.

Reason: Comparison not relevant to PICO (BCG vs no BCG)

Masood, S et al. T1G3 bladder cancer--indications for early cystectomy. International Urology & Nephrology 2004; 36(1): 41-44.

Reason: Non-comparative

Solsona, E et al. The optimum timing of radical cystectomy for patients with recurrent high-risk superficial bladder tumour. BJU International 2004; 94(9): 1258-1262.

Reason: Non-comparative

Chang, SS. Non-muscle-invasive bladder cancer: The role of radical cystectomy. Urology 2005; 66(5): 917-922.

Reason: Expert review

Nieder, AM et al. Radical cystectomy after bacillus Calmette-Guerin for high-risk Ta, T1, and carcinoma in situ: defining the risk of initial bladder preservation. Urology 2006; 67(4): 737-741.

Reason: Not relevant to PICO – all previous BCG

Stockle, M et al. Radical cystectomy--often too late? 1987. European Urology 2006; 50(6): 1132-1138.

Reason: Population not relevant –MIBC

Weiss, C et al. Radiochemotherapy after transurethral resection for high-risk T1 bladder cancer: an alternative to intravesical therapy or early cystectomy? Journal of Clinical Oncology 2006; 24(15): 2318-2324.

Reason: Non-comparative

Gautam, G and Kumar, R. T1 bladder cancer on restaging transurethral resection should be treated with immediate cystectomy. Indian Journal of Urology 2007; 23(2): 218

Reason: Not relevant to PICO

Raj, GV et al. Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. Journal of Urology 2007; 177(4): 1283-1286.

Reason: Not relevant to PICO

Inoue, M et al. Clinical outcome of chemoradiotherapy for T1G3 bladder cancer. International Journal of Urology 2008; 15(8): 747-750.

Reason: Non-comparative

Steen-Banasik, E et al. Brachytherapy versus cystectomy in solitary bladder cancer: a case control, multicentre, East-Netherlands study. Radiotherapy & Oncology 2009; 93(2): 352-357.

Reason: Not relevant to PICO – all T2 in RC group

Montgomery, JS, Weizer, AZ, and Montie, JE. T1 bladder cancer: advocating early cystectomy to improve oncologic control. Urologic Oncology 2010; 28(5): 466-468.

Reason: Expert review

Denzinger, S et al. Prognostic value of histopathological tumour growth patterns at the invasion front of T1G3 urothelial carcinoma of the bladder. Scandinavian Journal of Urology & Nephrology 2009; 43(4): 282-287.

Reason: Comparison not relevant to PICO

Park, J. Prognostic significance of the presence of proper muscle in the resected specimens of primary T1G3 bladder cancer. Korean Journal of Urology 2006; 47(2): 137-142.

Reason: Foreign language

Morelli, B. Which is the most suitable treatment of transitional bladder epithelium carcinoma G3 T1? Acta Urologica Italica 1992; 6(SUPPL. 4): 155-156.

Reason: Foreign language

Dunst, J et al. Radiochemotherapy for T1G3 bladder cancer. [Review] [16 refs]. Frontiers of Radiation Therapy & Oncology 2002; 36: 151-158.

Reason: Expert review

Hollenbeck, BK and Montie, JE. Early cystectomy for clinical stage T1 bladder cancer. Nature Clinical Practice Urology 2004; 1(1): 4-5.

Reason: Expert review

Kanayama, H-O. Bladder preservation therapy and total cystectomy for primary carcinoma in situ of the urinary bladder. Nishinihon Journal of Urology 1998; 60(5): 407-412.

Reason: Foreign language

Yates, DR and Catto, JW. Time to change our approach to high-risk nonmuscle-invasive bladder cancer management in the United Kingdom? Observations from the British Association of Urological Surgeons Cancer Registry. BJU International 2010; 106(5): 593-594.

Reason: Outcomes not relevant to PICO

Chang, SS. The adverse consequences of delaying radical cystectomy. Nature Clinical Practice Urology 2006; 3(6): 300-301.

Reason: Comment on study not relevant to PICO

Dinh, T. Compa rative effectiveness of conservative therapy versus cystectomy for non-muscle invasive bladder cancer patients. Value in Health 2013; Conference(var.pagings): 7

Reason: Abstract only

Huang, Y. Conservative treatment versus early radical cystectomy for T1G3 bladder cancer: A Meta-analysis. Tumor 2013; 33(10): 903-908.

Reason: Foreign language

Yu, L. Immediate cystectomy or conservative management for T1G 3 bladder cancer: A meta-analysis of general survival rate. Chinese-German Journal of Clinical Oncology 2013; 12(5): 243-245.

Reason: Meta-analysis not appropriate

Evidence tables

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Harland 2007 UK	Randomised trial 1991-2003	204 pT1G3NXM0 excluded prior BCG, IVT, widespread CIS and prior disease >T1	<table><tr><td></td><td>N (%)</td></tr><tr><td>Group 1 (single tumours no CIS)</td><td>76</td></tr><tr><td>Group 2 (multiple tumours or CIS)</td><td>128</td></tr><tr><td>Male</td><td>173 (85)</td></tr><tr><td>Female</td><td>31 (15)</td></tr><tr><td>Median age (IQR)</td><td>69 (63, 74)</td></tr><tr><td>WHO PS0</td><td>153 (75)</td></tr><tr><td>WHO PS1</td><td>47 (23)</td></tr><tr><td>WHO PS2</td><td>4 (2)</td></tr><tr><td colspan="2">Largest tumour diameter (cm)</td></tr><tr><td>2 or less</td><td>125 (64)</td></tr><tr><td>2.1-5</td><td>63 (32)</td></tr><tr><td>>5</td><td>6 (3)</td></tr><tr><td>Missing</td><td>10</td></tr></table>	Group 1: Radiotherapy Group 2: Radiotherapy – 3 or 4-field megavoltage irradiation to bladder only. 60Gy in 30 fractions during 6wks or equivalent	Group 1: Observation – no treatment other than TUR given before cystoscopy at 3mo Group 2: Intravesical therapy – 6-weekly MMC 40mg or BCG according to clinician preference. 2nd course of BCG given if follow-up biopsy was positive.	Median 44 mo (IQR 27 to 77)	**Progression-free interval,** 33/102 control vs 32/102 RT, HR 1.07 (0.65-1.74) **Progression-free survival,** median 66mo control vs 49mo RT, HR1.35 (0.92-1.98) **Overall survival,** median 88.5 control vs. 67mo RT, HR 1.32 (0.86-2.04) **Recurrence-free interval,** median 12.5mo control vs 16mo RT, HR 0.77 (0.54-1.10) **Recurrence-free survival,** median 12mo control vs 13mo RT, HR 0.94 (0.67-1.30) **Toxicity** Observation group, 4 (11%) urinary frequency, 1 (3%) cystitis. IVT group, 1 (2%) frequency, 1 (2%) tiredness. RT arms, 6(6%) telangiectasia, 8 (8%) frequency, 2 (2%) cystitis, 1 (1%) rectal bleeding, 1 (1%) diarrhoea, 5 (5%) long-term toxicity. **Cystectomy rate** Group 1, 14% (11), Group 2, 16% (20)	NR	ITT analysis performed. Central randomisation by MRC trials unit.
De Berardinis 2011	Retrospective cohort study 1995-2001	152 high risk NMIBC. Excluded recurrent	Mean age 70y (range 36-80). Male/female 110/42 (72%/28%) <table><tr><td></td><td>Group A</td><td>Group B</td></tr></table>	Group A (n=80): TURB + re-TURB +BCG (6-weekly instillations then	Group B (n=72): immediate RC with extended lymphadenectomy	Median 8.3 years	**Progression-free survival** BCG 25/80 (31%) median 25 months, RC 18/72 (25%) median 25.9 mo (p=0.380).	NR	RC group - 19 (26%) had pT2 or higher after RC and 4 (6%)

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Italy		tumours, >T1, PS 3-4, age >80yrs	<table><tr><td></td><td>n(%)</td><td>n(%)</td></tr><tr><td>T1G3 unifocal</td><td>21 (26)</td><td>19 (26)</td></tr><tr><td>T1G3 multifocal</td><td>33 (41%)</td><td>31 (42)</td></tr><tr><td>T1G3+CIS</td><td>26 (34)</td><td>23 (32)</td></tr></table>	3-yrs maintenance – 3 weekly instillations every 3 or 6 mo)			**Overall survival** BCG 34/80 (42.5%) median 55.3mo, RC 42/72 (58%) median 54.9mo (p=0.0487) **Cancer specific survival** BCG 18/80 (22.5%) median 47.5mo, RC 16/72 (22%) median 45.7mo (p=0.976). 20/25 patients that progressed in the BCG group had organ-confined disease and underwent RC. 5 had distant mets after median 18.2mo		had lymph node involvement. Possible confounding of survival by 20 BCG patients undergoing RC after disease progression.
Badalato 2012 USA	Retrospective review 1990-2010	349 high grade T1 TCC. 57 progressed from previous low-grade disease	<table><tr><td></td><td>RC n(%)</td><td>Control n(%)</td></tr><tr><td>Mean age</td><td>68</td><td>70</td></tr><tr><td>Male</td><td>88 (78)</td><td>168 (71)</td></tr><tr><td>Caucasian</td><td>76 (67)</td><td>171 (73)</td></tr><tr><td>Progressed to cT1</td><td>9 (8)</td><td>48 (20)</td></tr><tr><td>Year</td><td></td><td></td></tr><tr><td>1990-1999</td><td>54 (48)</td><td>36 (15)</td></tr><tr><td>2000-2010</td><td>59 (52)</td><td>200 (85)</td></tr></table>	Immediate RC (n=113) -within 90 days of diagnosis with no intervening TUR or IVT	Conservative treatment (n=236) - observation or any IVT	Median from diagnosis 43 mo RC group and 36mo control group	**Disease-specific survival** Control group better than RC (p=0.012) across both eras, but subgroup analyses this was only significant in 2000-2010 cohort where 5-yr survival 64% vs 85%, p=0.0075). Conservative management associated with improved DSS when controlling for LVI, age and prostatic urethral involvement HR 0.41 (0.21-0.82) No survival advantage for immediate or delayed RC cohorts (p=0.45 and 0.14).	NA	
Thalman 2004 Switzerland	Retrospective review 1980-1999	121 primary T1G3	<table><tr><td></td><td>RC n(%)</td><td>TUR+BCG n(%)</td></tr><tr><td>Number</td><td>29</td><td>92</td></tr><tr><td>M/F</td><td>26/3</td><td>71/21</td></tr></table>	Immediate RC (n=29): within 3mo of TUR. Indications were	BCG (n=92): minimum of 6 weekly instillations. 22%	Median 6.9 yrs (range 0.2-16.5)	**Progression:** 30/92 (33%) BCG vs 6/29 (21%) RC. Median 11.4mo (3-119) vs 13.2mo (5.5-37), p=0.09.	NA	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			Median age (range): 66 (42-75); 69 (37-88) CIS: 6 (21); 20 (22) Multifocal disease: 22 (76); 51 (55)	multifocal disease or residual tumour at 2nd TUR 12 (41%) had pT2 or higher	received 2+ 6-wk cycles. 27 (29%) underwent deferred RC for progression at a median of 12.9mo (4.8-136)		Median PFS not achieved in RC group, 134 mo in BCG group. **Disease-specific survival:** 21/92 (23%) BCG vs. 7/29 (24%) RC. 5-yr DSS 80% BCG vs 69% RC, p=0.33. **Overall survival:** 39/92 (43%) BCG vs. 14/29 (48%) RC. 5-yr OS= 69% BCG vs. 54% RC, p=0.124 **Deferred v immediate RC**: no difference in OS. 10/27 (37%) patients undergoing deferred RC died of disease at median 12.5mo (3-34). For DSS the difference was significant in favour of DRC (p=0.02).		
Patard 2001 France	Retrospective cohort study 1979-1996	94 T1G3	83 male/11 female. 35% already had TUR for previous NMIBC, 52% solitary tumour, 22% had more than 3 tumours. RC / TUR / BCG N: 14 / 30 / 50 Mean age: 63 / 67 / 63 Mean tumour size (mm): 20 / 20 / 27 Mean no. tumours: 1.9 / 2.1 / 1.9 Mean TUR rate before treatment: 0.42 / 0.86 / 0.74	Primary RC (n=14) 8 patients (57%) had MIBC in the operative specimen	TUR +BCG (n=50): 6-wk course of 75mg or 150mg BCG Pasteur 3-4 wks after initial TUR. TUR alone (n=30): 43% of these patients received BCG later during follow-up..	Mean 62 months	**Disease-free survival:** RC, 7/14 (50%) alive and disease-free at mean 94 months vs. 40/50 (80%) BCG at mean 65 mo and 10/30 (33%) TUR alone at mean 103 mo. Significant difference between BCG and TUR alone or RC groups (p=0.02). **Disease-specific mortality:** 6/14 (43%) RC mean 20mo vs. 7/50 (14%) BCG mean 33mo vs 7/30 (23%) mean 69 mo. No difference in cancer-specific death rates. 23 patients had delayed RC at a median interval of 16mo: 8	NA	

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>(34%) died of cancer at median 28mo.
Bladder preservation: 35/40 (87%) BCG treated patients and 11(36%) TUR only had intact bladder after mean 65mo follow-up. 15 BCG patients had RC.</td><td></td><td></td></tr>
<tr><td>Park 2009

Korea</td><td>Retrospective review

1989-2005</td><td>194 primary T1G3</td><td>170 M / 24 F, median age 63 yrs.

Patients having immediate RC were younger than surveillance (median age 60.5 vs 65) and had higher proportion of non-papillary tumours (41 v 62%) and tumours without proper muscle (26 v 42%)

34% of RC group were upstaged after RC</td><td>Immediate RC (n=50): based on patients age, tumour size, multiplicity, absence of muscle in TUR, patient willingness</td><td>Surveillance after TUR (N=144): 119 (83%) treated with BCG or MMC 2 wks after TUR. No maintenance BCG.</td><td>Median 52.5mo</td><td>Cancer-specific survival: 5-yr rate 95.6% BCG vs. 84% RC (p=0.005)
13.2% (19/144) of the surveillance group progressed.</td><td>NA</td><td>Age, non-papillary morphology, and absence of proper muscle predictive of DSS which may confound DSS results.</td></tr>
<tr><td>Dalbagni 2009

USA</td><td>Retrospective review

1990-2007</td><td>417 T1 high grade</td><td><table><tr><th></th><th>IRC n (%)</th><th>No IRC n(%)</th></tr><tr><td>Median age</td><td>67</td><td>65</td></tr><tr><td>Female</td><td>16 (19)</td><td>72 (22)</td></tr><tr><td>Any multifocal</td><td>20 (24)</td><td>90 (27)</td></tr><tr><td>Multifocal T1</td><td>9 (11)</td><td>35 (11)</td></tr><tr><td>Recurrence</td><td>6 (7)</td><td>28 (8)</td></tr><tr><td>CIS</td><td>15 (18)</td><td>84 (25)</td></tr><tr><td>High grade</td><td>84 (100)</td><td>317 (96)</td></tr><tr><td>Prior BCG</td><td>3 (4)</td><td>25 (8)</td></tr><tr><td colspan="3">Staging from restaging TUR</td></tr><tr><td><T1</td><td>26 (31)</td><td>234 (70)</td></tr><tr><td>T1</td><td>58 (69)</td><td>99 (30)</td></tr><tr><td colspan="3">Muscle in restaging TUR</td></tr><tr><td>No</td><td>72 (22)</td><td>25 (30)</td></tr><tr><td>Yes</td><td>261 (78)</td><td>59 (70)</td></tr></table></td><td>Immediate RC (n=84) within 3mo of restaging TUR

23% were pT2 or higher after RC</td><td>No immediate RC (n=333): BCG N=138,</td><td>Median 4.3 yrs</td><td>Disease specific survival: no difference between immediate RC and no immediate RC (p=0.7)
Overall survival: 5-yr OS 79% (95% CI 66-88%) IRC vs. 84% (78-88%) without IRC (ns)

Early BCG (n=138). 51/138 (37%) died overall, 29/138 (21%) died from bladder cancer

59/333 on surveillance had deferred RC – 20% for progression to MIBC, 61% for recurrent T1 tumours,19% for</td><td>NA</td><td>4% of IRC group had prior BCG</td></tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							lower than T1 recurrence No difference in survival between IRC and DRC (p=0.3)		
Iida 2009 Japan	Retrospective review 1991-2005	93 T1G3	Male: 74 (80%) Female: 19 (20%) Mean age: 74 (46-95) CIS+TaG3: 5 CIS+papillary T1G3: 20 CIS only: 3 T1G3 only: 65 Multifocal: 74 Solitary: 19	IVT n=71: 47 epirubicin, 24 BCG.	RC: n=22 (including 6 delayed cystectomy after several TUR and conservative therapy)	Median 68.7mo	91.7% of BCG group had complete response without need for further treatment. **Survival:** 1 cancer death in RC group vs. 19 deaths (15 cancer-related) in IVT group. Survival in RC group significantly higher than conservative therapy (p=0.04) **Cystectomy rate:** 21/69 (30%) epirubicin group and 1/24 (4%) BCG group RC after failure of IVT.	NA	
Hautman 2009 Germany	Retrospective review 1986-1998	274 T1G3	Not reported for T1G3	Early RC (n=175): within 90 days	Deferred RC (n=99): may have had BCG therapy and further TUR prior to RC	Mean 58 mo (range 0-271)	**Disease-specific survival:** 5-years 83.9% early RC vs. 74.8% deferred RC. 10-yr DSS 78.9% vs 64.5%, 15-yr DSS 76.1% vs 60.7% all in favour of early RC.	NA	
Wong 2009 UK	Retrospective review 1998-2007	77 high grade T1	Mean age 67.2±8.3 years. pT0: IRC 9/26 (25%); DRC 5/41 (12%) pTis: IRC 14 (36%); DRC 10 (24%) pTa: IRC 4 (11%); DRC 4 (10%) pT1: IRC 5 (14%); DRC 4 (10%) pT2+: IRC 4 (11%); DRC 18 (44%)	Early RC n=36	Delayed RC n=41, after BCG failure	Median 53 mo	**Overall survival:** 5-years (26/36) 72.2% v (30/41) 73.2% (p=0.75)	NA	Abstract only
Denzinger 2008 Germany	Retrospective review 1995-2005	105 T1G3 with two or more risk factors: large tumours	Early RC / D RC N: 54 / 51 Male: 32(59%) / 30(60%) Median age: 73.5 / 75.2 Multiple,: 23 (43%) / 24 (47%)	Early RC n=54, on average 4wk following initial TUR	Deferred RC n=51, all received 6-weekly BCG. RC for T1G3 recurrence (48%)	Median 5.4yr (range 0.9-12.5) for censored patients,	**Morbidity:** 7% major surgical complications (fatal pulmonary embolia (2), fatal cardiac ischaemia (1), impaired wound healing (4).	NA	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
		(>3cm), multifocal disease and/or CIS all offered RC	47/105 >3cm, 77/105: 42 (78%); 35 (69%) CIS, 48/105: 21 (39%); 27 (53%) No difference in upstaging between treatment groups. (early RC=14, deferred RC =18)		and/or CIS (38%), MIBC (34%). Median time to deferred RC=11.2 mo (range 3-19)	Median 5.1yr (range 0.4-12.5) non censored patients	Equally distributed between groups. **Disease-specific survival:** Early RC showed longer survival compared with deferred RC. 8% early RC and 24% deferred RC died of progressive disease. 5 and 10-yr survival were 83% and 78% early RC and 67% and 51% deferred RC (p<0.01) Deferred RC (HR 5.13, 1.62-17.08) most significant factor of cancer-related death, followed by CIS (HR 2.55, 1.21-12.89). CIS was significantly related to DSS in deferred RC only		
Ali-el-Dein 2011 Egypt	Retrospective review 1990-2004	204 T1, excluded MIBC after failure of IVT, cases that died from unrelated illness	Tumour multiplicity more common in deferred RC group. Groups were comparable regarding diversion after RC, lymph node status, postoperative morbidity, sites of local recurrence or distant mets. Primary RC / D RC N: 134 (66%); 70 (34%) Median age: 54; 55 M/F: 118/16; 66/4 G1: 12 (9%); 7 (10%) G2: 108 (80.6%); 49 (70%) G3: 14 (10%); 14 (20%) CIS: 36 (27%); 22 (31%)	Primary RC n=134	Deferred RC n=70, within 1mo of BCG or IVT failure (1 or 2 consecutive 6-wk courses)	Mean 79 mo (6-181) and 66 mo (6-190)	**Disease-specific survival:** 3-y / 5-y / 10-y PRC: 84% / 78% / 69% DRC: 79% / 71% / 64% No significant differences, p=0.25	NA	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Kamat 2006 USA	Retrospective review 1989-2004	44 NMIBC all with micropapillary TCC NMIBC	Mean age: 64.3 yrs Male: 41 (93%) Female: 3 (7%) cTa: 5 (11%) cTis: 4(9%) cT1: 35 (80%) Initial therapy: BCG: 27 (62%) RC: 12 (27%) Chemoradiation: 1 (2%) Surveillance: 4 (9%)	Primary RC n=12	Deferred RC n=18, after failed IVT	Range 1.7 – 181.2mo	**Disease-specific survival:** 5-yr Primary RC 72% vs. 60% deferred RC. No patients in deferred RC group survived 10-yr, 10-yr DSS in early RC was 72%. Median survival not reached in primary RC group and was 61.7mo in deferred RC group. Deferred RC group had higher incidence of non-organ confined disease and node-positive disease detected at RC than initial RC group. **Disease-related morbidity:** 2/12 (17%) early RC vs. 8/18 (44%) deferred RC died of bladder cancer	NA	All patients with MP features classified as having MP regardless of % of the MP component
Cheng 1999 USA	Retrospective review 1972-1979	138 urothelial CIS, no previous or coexisting TCC at time of diagnosis. 49 had history of non-invasive papillary TCC	Mean age: 65.6 yrs Male: 121 (88%) Female: 17 (12%) <3 tumours: 103 (75%) ≥3 tumours: 35 (25%)	N=41 immediate RC and 2 partial cystectomy	N=95, delayed RC (34), intravesical therapy (48), radiation therapy (19)	Mean after surgery 11 yrs (range 0.7-25)	**Progression-free survival:** 15-yr PFS 73% early vs. 50% no early, p=0.06 **Disease-specific survival:** 76% early vs. 72% no early, p=0.96 **Overall survival:** 61% early vs. 31% no early RC, p=0.001 Patient age predicted PFS and OS. After controlling for age there was no difference in OS between patients who underwent immediate RC and those who did not.	NA	Comparison group includes delayed RC patients and those who had IVT and RT only.
Van den Bosch 2011	Systematic review of observational	3088 patients from 19 studies (7 prospective,	Studies included if including at least 75 patients with high-risk NMIBC according to EAU guidelines: T1G3, multifocal or highly recurrent, CIS, who were initially	N/A Reported progression and	N/A	Median follow-up ranged from 52-123 mo in	**Progression:** 659/3088 (21%) progressed to MIBC (22% progression in prospective studies, 21%	NA	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
	studies	12 retrospective)	treated conservatively. (TURBT and intravesical instillations). Median follow-up of at least 48 months, reporting data on progression to MIBC and death from BCa. Last search was run on 30 January 2011.	DSS in high-risk NMIBC conservatively treated patients		prospective studies and from 48-107 mo in retrospective studies.	progression rate in retrospective studies) **Death from BCa:** 428/3088 (14%) died of BCa (15% prospective studies, 13% retrospective studies) **Disease-specific survival:** After progression to MIBC = 35% (32%, range 13-64, prospective studies, 37%, range 6-59 retrospective) Median DSS was 30% for prospective studies and 39% for retrospective studies. Studies with long (>60 mo) and short term (48-60mo) follow-up both had median DSS of 33%		
Fritsche 2010 1979-2008	Cohort study	1136 with T1G3. Excluding patients without muscle in TUR. No RT or neoadjuvant CT. No distant mets at time of RC. Re-TUR in nearly 70% of patients	Median age (range) yrs: 66.6 (29-94) Female: 220 (19.6%) Male: 901 (80.4%) Year of surgery 1979-1984: 47 (4.1%) 1985-1989: 79 (7%) 1990-1994: 94 (8.3%) 1995-1999: 255 (22.4%) 2000-2005: 477 (42%) 2006-2008: 182 (16%) Pathological stage pT0: 68 (6.1%) pTa: 42 (3.7%) pTis: 132 (11.7%) pT1: 325 (28.8%) pT2: 239 (21.1%) pT3: 219 (19.4%)	N/A Reports recurrence, OS and disease-specific mortality in T1G3 patients treated with RC and bilateral lymphadenectomy	N/A	Median 48 mo (range 0.4-299.9)	**Recurrence:** 22.5% in 2yr, 31.9% in 5yr, 34.5% in 8yr **Death from bladder cancer:** 7.3% in 2yr, 29.8% in 5 yr, and 35.5% in 8yr **Overall mortality:** 8% in 2yr, 44% in 5yr, 53% in 8yr In univariate analysis, Older age at RC, pathologic stage, stage discrepancy, tumour grade, STSM, LVI, LNstatus and no. of +ve LNs were associated with disease recurrence and death from bladder cancer. In multivariate analyses, LN		Not reported whether RC was primary treatment.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			pT4: 102 (9.1%) >pT1: 560 (49.7%) Non-organ confined: T3/4 and/or N+: 376 (33.4%) G0: 68 (6.1%) G1: 24 (2.1%) G2: 487 (43.4%) G3: 542 (48.3%) CIS absent: 532 (47%) CIS present: 601 (52%) STSM absent: 1056 (93.7%) STSM present: 71 (6.3%) LVI absent: 828 (75.7%) LVI present: 266 (24.3%) LN mets absent: 914 (83.2%) LN mets present: 184 (16.2%) Adj chemo: 175 (15.5%) No chemo: 953 (84.5%)				status, no. of +ve LNs, LVI and pathological stage were associated with recurrence and death from bladder cancer.		
Canter 2013 USA	Retrospective cohort study 2004-2007	8467 with clinical high grade T1 (Grade 3 or 4) urothelial BCa identified from SEER database	No RC (n=8070) / RC (n=397) Mean age: 73.1 / 67.1 male: 77% / 80% female: 23% / 20% Married: 61% / 71%	RC (n=397) within 1 year of diagnosis	No RC (n=8070) no details about treatment provided.	NR	**Overall survival:** 1, 2, 3 year for patients who had RC = 91%, 88%, 82%. For those without RC = 77%, 78%, 68% (p=0.004). **Bladder cancer death:** 1, 2, 3 year for patients who had RC = 4%, 8%, 10%. For those without RC = 4%, 10% and 12% (p=0.134)	NR	No data in SEER registry about date of surgery, previous tumours, or certain clinic pathologic data.

Health Economic Evidence: What are the comparative patient outcomes for treating high-risk non-muscle invasive bladder cancer with radiotherapy, intravesical BCG or radical cystectomy with urinary stoma or bladder reconstruction?

Review question

For which patients with non-muscle invasive bladder cancer would primary cystectomy produce better outcomes than BCG?

Table 79: Pico Table For Treating High Risk Non-Muscle Invasive Bladder Cancer

Population	Intervention	Comparison	Outcomes
Patients diagnosed with high risk NMIBC with no prior BCG therapy Subgroups: • male/female • Pathology features • Solitary tumour • Multifocal tumour • Extent of Lamina propria involvement • Presence of CIS	Primary Cystectomy Primary Radiotherapy/chemoradiotherapy	BCG therapy	• Overall survival • Disease-specific survival • Metastasis free survival • Bladder preservation rates • treatment related mortality • treatment related morbidity • Health-related quality of life, inc patient reported outcomes

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO

- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

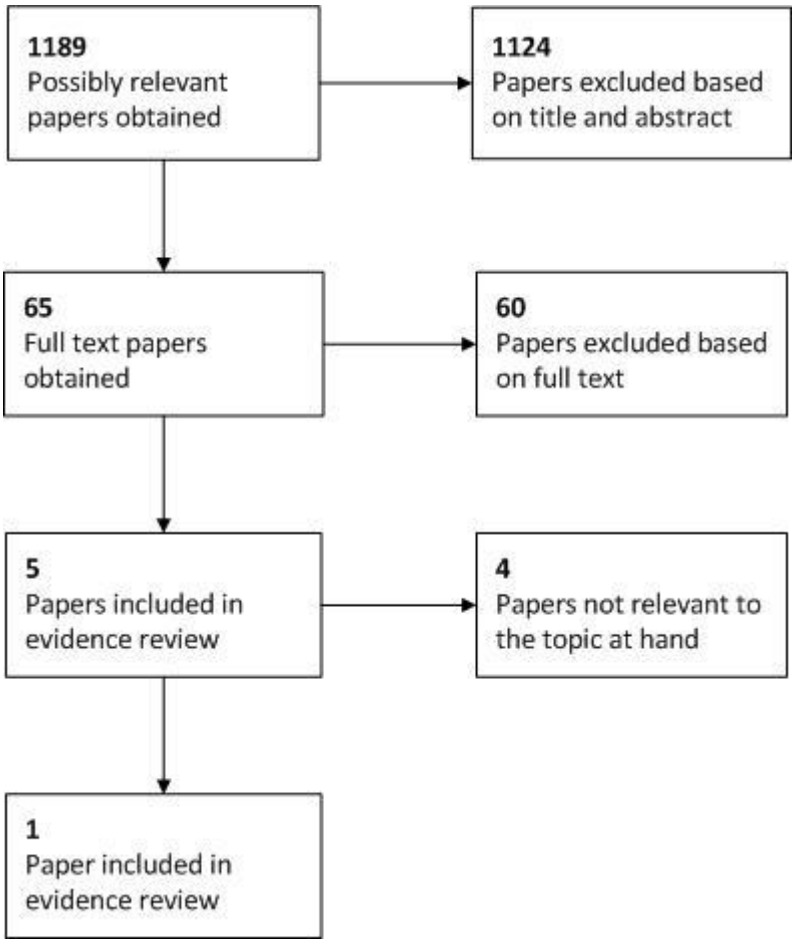
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

Three searches for economic evidence were run over the development of the guideline; one at the start of the process, an update midway through and a further update at the end of the process. The diagram below shows the combined results of the three searches and illustrates the sifting process.

Figure 51: Summary Of Evidence Search And Sifting Process For This Topic



It can be seen that, in total, 1,189 possibly relevant papers were identified. Of these, 1,124 papers were excluded at the initial sifting stage based on the title and abstract while 65 full papers were obtained for appraisal. A further 56 papers were excluded based on the full text as they were not

applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, nine papers were included in the systematic review of the economic evidence for this guideline.

One of these nine papers related to the topic at hand and was thus included in the review of published economic evidence for this topic; Kulkarni et al. 2009. The study included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

Quality and applicability of the included study

The study was only partially applicable to the decision problem that we are evaluating, primarily because it was a Canadian study and as such the estimated costs and benefits might not apply to the UK health care setting. In addition, quality of life values were not all reported directly from patients and were often not drawn from bladder cancer patients (data from prostate, lung and breast cancer patients)

Potentially serious limitations were also identified with the analysis. Although a systematic literature review was conducted, the evidence identified and utilised was not always of high quality. The costs applied in the model were not always sourced from patients with bladder cancer e.g. chemotherapy costs were based on patients with non-small cell lung cancer. In addition, while PSA and scenario analyses were performed, further sensitivity analyses could have been conducted to better explore uncertainty.

Table 80: Table Showing Methodological Quality And Applicability Of The Included Study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		
Potentially serious limitations		Kulkarni et al. 2009
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Kulkarni et al. 2009 are summarised in the modified GRADE table below.

Table 81: Modified Grade Table Showing The Included Evidence For Treatments For High Risk Non-Muscle Invasive Bladder Cancer

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Kulkarni et al. 2009	Men with incident, high-risk, T1G3 bladder cancer.	**"BCG" -** Initial conservative therapy, which consisted of intravesical BCG with possible delayed cystectomy	$42,600	10.60 LYs 9.39 QALYs	Reference			**Scenario analyses** Several scenario analyses were conducted in which age and co-morbid status was varied. The results showed that regardless of co-morbid status, immediate cystectomy ws found to be the dominant strategy in patients aged ≤55 years old. At ≥70 years, conservative therapy was either dominant or had an ICER that was likely to be considered cost-effective (≤$32,700 per QALY). Between ages 60 and 70 years, the optimal choice was dependent upon co-morbidities, with increased co-morbid burden making	**Partially applicable** Not a UK study (Canadian), thus estimated costs and benefits might not apply to UK health care setting. Quality of life values were not all patient reported and were often not drawn from patients with bladder cancer (data from prostate, lung and breast cancer patients was used). **Potentially serious limitations** Although systematic literature review was conducted, evidence identified and utilised was not always of high quality. Costs were not always sourced from patients with bladder cancer. For instance chemotherapy costs were based on patients with non-small cell lung cancer While PSA and scenario
		"Cystectomy" - immediate nerve sparing radical cystectomy with an orthotopic ileal neobladder	$37,600	11.01 LYs 9.46 QALYs	-$5,000	0.41 LYs 0.07 QALYs	Cystectomy is dominant using both effectiveness measures		

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
								conservative therapy more cost-effective. **Probabilistic sensitivity analyses (PSA)** PSA was conducted using 1000 2nd order Monte Carlo simulations. The immediate cystectomy strategy was found to be cost-effective in 70% and 67% of simulations at thresholds of $20,000 and $50,000 per QALY, respectively.	analyses were performed, further sensitivity analysis could have been conducted to better explore uncertainty.
	Comments:								

Evidence statements

The base case results of the cost-effectiveness analysis showed that immediate cystectomy was cheaper and more effective than conservative therapy (BCG with possible delayed cystectomy) i.e. immediate cystectomy was found to be the dominant strategy.

Scenario analyses, in which age and co-morbid status were varied, showed that the optimal strategy is likely to be different for different patient subgroups. The analysis showed that immediate cystectomy was dominant in patients aged ≤55 years old regardless of co-morbid status. For patients ≥70 years old, conservative therapy was either dominant or had an ICER that was likely to be considered cost-effective (≤$32,700 per QALY). For patients between ages 60 and 70 years old, the optimal choice was dependent upon co-morbidities, with increased co-morbid burden making conservative therapy more cost-effective.

The probabilistic sensitivity analyses (PSA) showed that immediate cystectomy was found to be cost-effective in 70% and 67% of simulations at thresholds of $20,000 and $50,000 per QALY, respectively.

The results suggest that, compared with a conservative strategy using BCG, immediate radical cystectomy yielded better outcomes and lower costs for the *average* patient. Furthermore, the results suggest that tailoring therapy based on patient age and co-morbidity may increase survival and yield significant costs savings for the health care system.

However, there are reservations about the applicability of the analysis because it considered the Canadian health care system which may not reflect the UK setting. There were also concerns about the quality of life data that were used as they were not all patient reported and were often not drawn from patients with bladder cancer (data from prostate, lung and breast cancer were used). Potentially serious limitations were also identified as, although a systematic literature review was conducted, some of the evidence informing the model was not considered to be of high quality. Furthermore, costs were not always sourced from patients with bladder cancer, such as chemotherapy costs, which were based on patients with non-small cell lung cancer.

References

1. Kulkarni, G. S., et al. "Cost-effectiveness analysis of immediate radical cystectomy versus intravesical Bacillus Calmette-Guerin therapy for high-risk, high-grade (T1G3) bladder cancer (Structured abstract)." Cancer 115.23 (2009): 5450-59.

Full evidence table

The full details of the study included in the evidence review are presented in the evidence table below.

Table 82: full evidence table showing the included evidence (Kulkarni et al. 2009) for treatments for high risk non-muscle invasive bladder cancer

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Kulkarni et al. **Year:** 2009 **Country:** Canada	**Type of analysis:** Cost-utility analysis (CUA). **Model structure:** Markov Monte-Carlo cost-effectiveness model. **Cycle length:** 6 months (reflects intervals when treatment decisions are made for patients with bladder cancer). **Time horizon:** Lifetime analysis. Mean survival of 14.61 years and 13.89 years with immediate cystectomy and conservative BCG therapy respectively. **Perspective:** Third party payer **Source of base-line data:** The base case analysis assumes that patients have no comorbidities. However, numerous	**Inclusion criteria:** Incident, high risk, T1G3 bladder cancer. **Exclusion criteria:** Not reported. **Base case (population):** Hypotherical cohort of potent men with incident, high-risk, T1G3 bladder cancer. **Sample size:** 1000 Monte-Carlo simulations were run (base case analysis appears to be based on the mean of these probabilistic runs).	Two treatment strategies were compared: A. Immediate nerve sparing radical cystectomy with an orthotopic ileal neobladder ("Cystectomy") B. Initial conservative therapy, which consisted of intravesical BCG with possible delayed cystectomy ("BCG")	**Effectiveness (LYs):** *Undiscounted* Cystectomy BCG Incremental *Discounted* Cystectomy BCG Incremental **Effectiveness (QALYs):** *Undiscounted* Cystectomy BCG Incremental *Discounted* Cystectomy BCG Incremental **Total costs** *Undiscounted* Cystectomy BCG	**Total (SD)** 14.61 (1.43) 13.89 (1.49) 0.72 11.01 (0.90) 10.60 (0.95) 0.41 12.62 (2.69) 12.24 (2.03) 0.38 9.46 (1.92) 9.39 (1.34) 0.07 $42,500 ($1,700) $50,100 ($3,500)	**Funding:** Kulkarni is supported by a Canadian Institutes for Health Research fellowship. **Comments** Model used in analysis was previously described in another published paper by the authors (Kulkarni et al. 2007). This study focused on the patient's age,

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	scenarios based on comoridities were evaluated in the model. These scenarios were based on relative risks that were sourced from published studies. Age-specific risk of dying from other causes was sourced from actuarial life tables. **Source of effectiveness data:** Probabilities associated with each treatment strategy were obtained from both RCTs and retrospective cohort studies. Each study was analysed for every possible probability in the model. Where multiple sources were identified, probabilities were calculated by weighting each article's probability by its sample size. However, if one of the studies was adjudged to be of higher quality than the other sources, then the higher quality values were used.	**Age:** Analysis based on a reference case using a 60 year old patient. **Gender:** Analysis based on a reference case using a male patient. **Subgroup analysis:** Subgroups based on age and comorbid status were explored in scenario analysis.		Incremental *Discounted* Cystectomy BCG Incremental **ICER:** Cost per LY Cost per QALY **Uncertainty:** **Scenario analyses** Several scenario analyses were conducted in which age and comorbid status were varied: ***No comorbidity*** Age = 55 Age = 60 Age = 65 Age = 70 Age = 75 Age = 80	-$7,600 $37,600 ($1,300) $42,600 ($3,400) -$5,000 Cystectomy dominant Cystectomy dominant **ICER (cost/QALY)** Cystectomy dominant Cystectomy dominant Cystectomy dominant $32,700 $7,700 BCG dominant	comorbid status and preferences to decide upon the optimal management of high risk T1G3 bladder cancer. Note that costs and cost-effectiveness were not considered in this study.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Probabilities include treatment related complications (including operative mortality in cystectomy), progression and recurrence. **<u>Source of utility data:</u>** Authors state that the medical literature lacks detailed utility data for bladder cancer. Thus, utility scores sourced from other conditions in which similar states of health could be expected or from estimations from health care professionals. The utility associated with an uncomplicated, post-cystectomy health state was derived from a standard gamble involving 25 urologists at the author's institution (University of Toronto). Impotence and genitourinary complications were obtained from a decision analysis in prostate cancer (Alibhai et al. 2003). Utility of long term gastrointestinal			***Mild comorbidity*** Age = 55 Age = 60 Age = 65 Age = 70 Age = 75 Age = 80 ***Moderate comorbidity*** Age = 55 Age = 60 Age = 65 Age = 70 Age = 75 Age = 80 **Probabilistic sensitivity analysis (PSA)** PSA was performed using 1000 2nd order Monte-Carlo simulations. Results were presented in 3 ways: ***95% credible intervals were presented along with mean outcomes.***	 Cystectomy dominant Cystectomy dominant $16,400 BCG dominant BCG dominant BCG dominant Cystectomy dominant BCG dominant BCG dominant BCG dominant BCG dominant BCG dominant	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	complications post-cystectomy was taken from patients who have undergone ileal reservoir creation as a proxy for ileal neobladder patients. Short-term, post-operative utility of undergoing cystectomy was adapted from utilities measured for abdominal hysterectomy, colostomy creation for nonsevere trauma and radical prostatectomy. Utilities associated with metastases were assigned based on a patient's responsiveness to chemotherapy (i.e. responsive and unresponsive health states). Both of these values were sourced from published literature on breast cancer. Utilities for induction BCG, maintenance BCG and surveillance cystoscopy were based on published utilities associated with moderately invasive procedures, such as cardiac catheterization.			**<u>Effectiveness (discounted QALYs):</u>** Cystectomy BCG Incremental **<u>Total costs (discounted):</u>** Cystectomy BCG Incremental ***Graphed results using a cost-effectiveness acceptability curve (CEAC)*** The proportion of simulations that were cost-effective at various thresholds were presented: Threshold = $20,000 per QALY Threshold = $50,000 per QALY Threshold = $100,000 per QALY ***Value of additional information was estimated using expected***	**Mean (95% CrI)** 9.46 (3.98 to 11.90) 9.39 (6.16 to 11.49) 0.08 (-2.58 to 1.43) $37,600 ($35,000 to $40,200) $42,400 ($34,800 to $47,500) -$4,800 (-$3,000 to -$9,600) **Proportion cost-effective** 70% 67% 66%	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Utility of living with undiagnosed locally recurrent bladder cancer was not modelled. Utility of diagnosis of a recurrent lesion on BCG therapy was incorporated in the utility for a cytoscopy and utility of treatment of recurrent lesions was incorporated by assigning a disutility for TURBT. Chemotherapy disutility was adapted from breast and small cell lung cancer patients. **Source of cost data:** Inpatient and procedure costs were obtained from the University Health Network Case Costing Center, a large, high bladder cancer volume tertiary teaching hospital in Toronto Canada. Unit costs for long-term operative complications, such as bowel obstruction, ureteral stenosis, and incisional hernia. Authors state that chemotherapy costs for bladder cancer are not			***value of perfect information (EVPI) analysis*** At a threshold of $50,000 per QALY, the EVPI was estimated to be $28,220 per patient. With approximately 65,000 incident bladder tumours diagnosed annually in North America, of which 15% are high risk T1G3 lesions, perfect information would be valued between $18.3 million (quality unadjusted) and $275 million (quality adjusted).		

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	currently available. Thus, they instead used gemcitabine / cisplatin costs from a multinational costing study in nonsmall cell lung cancer. Chemotherapy related complications and medical oncology workload between the two diseases were also assumed to be similar. Costs of dying from cancer or other causes were extrapolated from on an ongoing comprehensive case-costing study for prostate cancer (unpublished). Costs incurred in the final 6 months of life were included. Physician service fees and drug costs were obtained from the 2005 Ontario Schedule of Benefits and the Ontario Drug Benefits Formulary / Comparative Drug Index, 39th edition (2005) and from the University Health Network outpatient pharmacy. **Currency unit:** Canadian dollars ($)					

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Cost year: 2005 **Discounting:** Costs and benefits discounted at a 3% per annum.					

4.3.2 Treatment following failure of BCG

Review question: What is the optimum treatment for patients with non-muscle invasive bladder cancer who have failed BCG?

Rationale

Intravesical BCG is an immunotherapy used to treat intermediate and high-risk non-muscle invasive bladder cancer. This therapy may be administered as either a single 6 week course (known as "induction BCG") or as repeated instillations episodically for several years (known as "maintenance BCG"). Each treatment includes the instillation of live BCG bacteria, of which various strains are known to exist, into the bladder. Failure to respond to BCG occurs when a further bladder cancer arises following or during BCG treatment. These cancers may be better, similar or worse to the original tumour, and may be detected during, shortly after, or many years following BCG treatment. Therefore the term BCG failure includes a wide spectrum of events. It can also include patients who did not complete their treatment due to BCG related side effects (called BCG intolerant). In general most physicians agree that the development of tumour with muscle invasion following or during BCG treatment requires radical treatment - either bladder removal (cystectomy) or radiotherapy, if cure is to be obtained. In contrast, there is less consensus regarding the treatment of BCG failure when the disease is not muscle invasive. Some physicians feel that the timing of failure (early versus late) is important, whilst other feel that failure at any time requires more aggressive treatment.

Whilst radical cystectomy is perceived as the gold standard treatment for BCG failure, it may be over treatment in some patients and other patients are keen to avoid bladder removal regardless of risks. Therefore "bladder-sparing" treatments are reported for use in this context. These include immunotherapies (e.g. repeated BCG instillations with or without additional immune modulator), intravesical chemotherapy (such as gemcitabine), device assisted intravesical chemotherapy (e.g. mitomycin-c administration using EDMA or hyperthermia) and radiotherapy. These approaches avoid removal of the bladder, but carry the risk that the tumour may not respond and will progress to invasion or spread beyond the bladder. They also have side effects and toxicity. Given the spectrum of events encompassed by the term BCG-failure, it is possible that different treatments will be better for different types of failure.

This review will compare different treatments for patients who fail BCG. It will identity the risks and benefits of each treatment and try to identify if some are more suited to certain types of BCG failure.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients diagnosed with NMIBC who have failed BCG Subgroups: - Male/female - Pathology features - Solitary tumour - Multifocal tumour - Extent of Lamina propria involvement	Intravesical chemotherapy Radiotherapy/ chemoradiotherapy Cystectomy BCG therapy Interferon Cystoscopy	Each other	• Overall survival • Disease-specific survival • Metastasis free survival • Bladder preservation rates • Treatment related mortality • Treatment related morbidity • Health-related quality of

- Presence of CIS			life, inc patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (DJ) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. A second sift of the literature was conducted by another reviewer (JH) and any disagreement between reviewers was discussed. Randomised trials and comparative studies were selected.

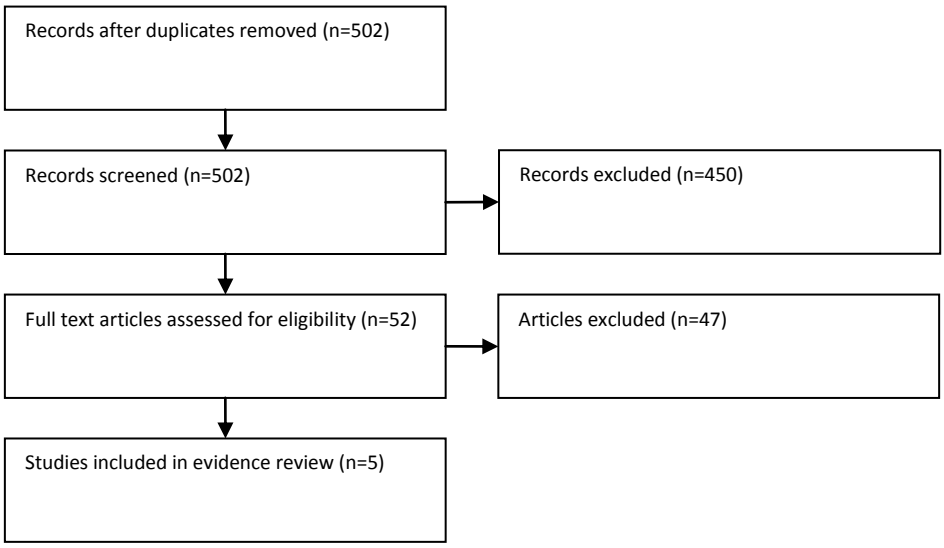
Data synthesis

Data was synthesised using GRADE. Meta-analysis was not possible for this review.

RESULTS

Result of the literature searches

Figure 55. Study flow diagram



Study quality and results

The evidence is summarised in GRADE evidence profiles (Tables 83-86)

Evidence statements

Gemcitabine versus Mitomycin C

Moderate quality evidence from one randomised trial (Addeo et al., 2009) of 109 patients suggests uncertainty over the incidence of tumour recurrence in gemcitabine- versus mitomycin C-treated

patients. Although incidence of tumour recurrence was lower in gemcitabine treated patients after 36 months of follow up, the 95% confidence interval around the estimated effect included both no effect and considerable benefit for gemcitabine.

Moderate quality evidence from one randomised trial of 109 patients (Addeo et al., 2009) suggests uncertainty over the incidence of tumour progression in gemcitabine- versus mitomycin C-treated patients. Incidence of tumour progression was lower in gemcitabine treated patients after 36 months of follow up, but the 95% confidence interval around the estimated effect was wide and included considerable harm, no effect and considerable benefit for gemcitabine.

Moderate quality evidence from one randomised trial of 109 patients (Addeo et al., 2009) suggested that gemcitabine treatment was associated with fewer adverse events than mitomycin C.

Gemcitabine versus BCG

Two studies (Di Lorenzo et al., 2009; Gacci et al., 2006) compared the effectiveness of gemcitabine to BCG. Meta-analysis of the results was not possible due to differences in study design and outcome definitions.

Moderate quality evidence from one randomised trial of 80 patients (Di Lorenzo et al., 2009) suggests that the incidence of tumour recurrence after 12 months is lower in patients treated with gemcitabine compared to treatment with BCG. In patients experiencing recurrence (n=56), there was no significant difference between treatment groups in the incidence of cystectomy due to disease progression. The incidence of grade two and grade three adverse events was similar for both treatments.

Very low quality evidence from one observational trial of 19 patients (Gacci et al., 2006) found no significant difference in tumour recurrence, overall survival, bladder preservation rates or adverse events between gemcitabine and BCG treatment.

BCG versus chemotherapy (MMC or epirubicin)

Very low quality evidence from one observational trial of 183 patients (Matsumoto et al., 2012) suggests that rates of recurrence-free survival (after five years of follow up) are greater in patients treated with BCG than in patients treated with chemotherapy (MMC or epirubicin).

BCG versus BCG plus interferon α2B

Very low quality evidence from one observational trial of 139 patients (Prasad et al., 2009) suggests that the incidence of disease recurrence is lower in patients treated with BCG alone compared with BCG in combination with interferon α2B.

Table 83. GRADE evidence profile: mitomycin C compared to gemcitabine for patients diagnosed with NMIBC who have failed BCG

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mitomycin C	Gemcitabine	Relative (95% CI)	Absolute	
Incidence of recurrence (follow-up median 36 months; assessed with positive cytoscopy)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	none	22/55 (40%)	15/54 (27.8%)	RR 1.44 (0.84 to 2.47)	122 more per 1000 (from 44 fewer to 408 more)	⊕⊕⊕O MODERATE
Number of patients with tumour progression (follow-up median 36 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	10/55 (18.2%)	6/54 (11.1%)	RR 1.64 (0.64 to 4.19)	71 more per 1000 (from 40 fewer to 354 more)	⊕⊕⊕O MODERATE
Number of patients developing metastases (median follow-up 36 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	1/55 (1.8%)	1/54 (1.9%)	RR 0.98 (0.06 to 15.3)	0 fewer per 1000 (from 17 fewer to 265 more)	⊕⊕OO LOW
Overall survival											
0	No evidence						-	-	-	-	
Bladder preservation rates											
0	No evidence						-	-	-	-	
Incidence of adverse events (follow-up median 36 months)[4]											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40/55 (72.7%)	21/54 (38.9%)	RR 1.87 (1.29 to 2.71)	338 more per 1000 (from 113 more to 665 more)	⊕⊕⊕O MODERATE
Treatment related mortality											
0	No evidence						-	-	-	-	
Treatment related morbidity											
0	No evidence						-	-	-	-	
Health related quality of life											
0	No evidence						-	-	-	-	

[1] Total number of events is less than 300.

[2] 95% confidence interval around the relative effect includes both no effect and appreciable benefit.

[3] 95% confidence interval around the relative effect includes no effect, appreciable benefit and appreciable harm.

[4] Proportion of adverse events deemed related to treatment was not reported.

Table 84. GRADE evidence profile: gemcitabine compared to BCG for patients diagnosed with NMIBC who have failed BCG

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine	BCG	Relative (95% CI)	Absolute	
Overall mortality (follow-up median 15 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	0/40 (0%)	1/40 (2.5%)	RR 0.33 (0.01 to 7.95)	17 fewer per 1000 (from 25 fewer to 174 more)	⊕⊕OO LOW
Incidence of tumour recurrence (follow-up 12 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21/40 (52.5%)	35/40 (87.5%)	RR 0.6 (0.44 to 0.82)	350 fewer per 1000 (from 157 fewer to 490 fewer)	⊕⊕⊕O MODERATE
Time to first recurrence (median follow-up 15 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	21/40 (52.5%)	35/40 (87.5%)	HR 1.1 (0.8 to 1.2)	3.9 months (GEM group) vs 3.1 months (BCG group)	⊕⊕⊕O MODERATE
Incidence of cystectomy due to disease progression in patients with recurrent disease											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,3]	none	7/21 (33.3%)	13/35 (37.1%)	RR 0.9 (0.43 to 1.89)	37 fewer per 1000 (from 212 fewer to 331 more)	⊕⊕⊕O MODERATE
Incidence of grade 2 adverse events											
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,3]	none	12/40 (30%)	13/40 (32.5%)	RR 0.92 (0.48 to 1.77)	26 fewer per 1000 (from 169 fewer to 250 more)	⊕⊕⊕O MODERATE
Incidence of grade 3 adverse events											
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	3/40 (7.5%)	3/40 (7.5%)	RR 1 (0.21 to 4.66)	0 fewer per 1000 (from 59 fewer to 275 more)	⊕⊕OO LOW
Overall mortality (follow-up median 15 months)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	0/9 (0%)	2/10 (20%)	RR 0.22 (0.01 to 4.05)	156 fewer per 1000 (from 198 fewer to 610 more)	⊕OOO VERY LOW
Incidence of tumour recurrence (follow-up 12 months)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	6/9 (66.7%)	5/10 (50%)	RR 1.33 (0.62 to 2.89)	165 more per 1000 (from 190 fewer to 945 more)	⊕OOO VERY LOW
Bladder preservation rate											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,3]	none	7/9 (77.8%)	6/10 (60%)	RR 1.30 (0.7 to 2.4)	180 more per 1000 (from 180 fewer to 840 more)	⊕OOO VERY LOW
Incidence of adverse events											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine	BCG	Relative (95% CI)	Absolute	
1[4]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	2/9 (22.2%)	3/10 (30%)	RR 0.74 (0.16 to 3.48)	78 fewer per 1000 (from 252 fewer to 744 more)	⊕OOO VERY LOW
Metastasis free survival											
0	No evidence						-	-	-	-	
Treatment related mortality											
0	No evidence						-	-	-	-	
Treatment related morbidity											
0	No evidence						-	-	-	-	
Health related quality of life											
0	No evidence						-	-	-	-	

[1] Total number of events was less than 300.
[2] Total population size was less than 400.
[3] 95% confidence interval around the relative effect includes appreciable harm, no effect and appreciable benefit
[4] Proportion of adverse events deemed related to treatment was not reported.

Table 85. GRADE evidence profile: BCG compared to chemotherapy for patients diagnosed with NMIBC who have failed BCG

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BCG**	**Chemotherapy**	**Relative (95% CI)**	**Absolute**	
Recurrence free survival (median follow-up 5.1 years)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/119 (59.7%)	5/24 (20.8%)	RR 2.89 (1.29 to 6.33)-	208 fewer per 1000 (from 208 fewer to 208 fewer)	⊕OOO VERY LOW
Overall survival											
0	No evidence						-	-	-	-	
Disease specific survival											
0	No evidence						-	-	-	-	
Metastasis free survival											
0	No evidence						-	-	-	-	
Bladder preservation rates											
0	No evidence						-	-	-	-	
Treatment related mortality											
0	No evidence						-	-	-	-	
Treatment related morbidity											
0	No evidence						-	-	-	-	
Health-related quality of life											
0	No evidence						-	-	-	-	

[1] Patients' treatment was based on clinician preference. Higher risk patients may have been disproportionately assigned to BCG treatment.

[2] Total number of events was less than 300.

Table 86. GRADE evidence profile: BCG alone compared to BCG plus interferon α2B for patients diagnosed with NMIBC who have failed BCG

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	BCG + IFN α2B	Relative (95% CI)	Absolute	
Disease recurrence (median follow-up 55.6 months)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	65/114 (57%)	21/25 (84%)	RR 0.68 (0.54 to 0.86)	269 fewer per 1000 (from 118 fewer to 386 fewer)	⊕OOO VERY LOW
Overall survival											
0	No evidence						-	-	-	-	
Disease specific survival											
0	No evidence						-	-	-	-	
Metastasis free survival											
0	No evidence						-	-	-	-	
Bladder preservation rates											
0	No evidence						-	-	-	-	
Treatment related mortality											
0	No evidence						-	-	-	-	
Treatment related morbidity											
0	No evidence						-	-	-	-	
Health related quality of life											
0	No evidence						-	-	-	-	

[1] Total number of events was less than 300.

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Reason for exclusion: Non-comparative study

Evidence tables

Study, country

Addeo et al, 2010
Italy

Study type, study period

Randomised controlled trial.
Patients enrolled between March 2003 and November 2005.

Number of patients

120

Patient characteristics

Inclusion criteria: patients with a history of superficial bladder cancer (Ta or T1 of any grade), whose disease had either progressed or relapsed after BCG treatment, or who were ineligible for BCG treatment.
Baseline characteristics:

	MMC (n = 55)	GEM (n = 54)
Male	47	46
Mean age, yrs	67.9	64.9
Recurrent single tumour	34	29
Recurrent multiple tumours	21	25
Largest tumour < 2 cm	33	36
Largest tumour > 2 cm	22	18
Stage Ta	35	37
Stage T1	20	17
Grade 1	14	11
Grade 2	27	28
Grade 3	14	15
Previous BCG treatment*	45	46

*Patients intolerant to BCG received previous epirubicin treatment.

Intervention

Mitomycin C 40 mg in 50 ml saline retained for one hour before voiding; no positional changes allowed. Early infusion within 2 days of TUR followed by 4 weekly treatments.
Initial responders who remained free of recurrences received maintenance therapy consisting of 10 monthly treatment during the first year.

Comparison

Gemcitabine 2,000 mg in 50 ml saline retained for one hour before voiding with no positional changes allowed. 6 week induction course of infusion.
Initial responders who remained free of recurrences received maintenance therapy consisting of 10 monthly treatment during the first year.

Length of follow-up

Median 36 months

Outcome measures and effect size

	MMC (n = 55)	GEM (n = 54)	P
Patients free of recurrence at end of follow up	33 (61%)	39 (72%)	-
Median time to tumour recurrence, months	15.0	Not reached	-
Relative risk of recurrences	0.94	0.72	0.291
Recurrence rate per 100 patient months	1.72	1.26	0.31
Patients with tumour progression by stage	10	6	0.140
Number of patient developing metastases	1 (1.8%)	1 (1.9%)	
Incidence of adverse events*	40 (72.2%)	21 (38.8%)	0.021
*dysuria, suprapubic pain, haematuria, chemical cystitis, local reactions, skin reaction.			

Source of funding

Not reported. All authors indicated no conflicts of interest.

Risks of bias

Selection bias: low risk.
Performance bias: low risk
Attrition bias: low risk
Detection bias: low risk

Additional comments

Participant flow inconsistently reported. 120 patients assessed for study eligibility; results reported for 109 patients. Of the 11 patients not analysed, it is unclear how many were randomised to a treatment group and/or received any treatment.

Study, country

Di Lorenzo, 2009
Italy

Study type, study period

Randomised controlled trial.

June 2006 to May 2008.

Number of patients

80

Patient characteristics

Inclusion criteria: patients with high risk NMIBC failing BCG, where radical cystectomy was indicated but refused or inappropriate.
Baseline characteristics:

	GEM (N = 40)	BCG (N = 40)
Male	27	22
Mean age, yrs	69.3	71.4
Stage Ta	10	8
Stage T1	30	32
Low Grade	11	13
High grade	29	27
Single tumour	10	8
Multiple tumours	30	32
Tumour < 3 cm	15	17
Tumour > 3 cm	25	23

Intervention

Intravesical gemcitabine (2,000 mg/50 ml) twice weekly for 6 weeks then once weekly for 3 weeks at 3, 6 and 12 months.

Comparison

Intravesical BCG (81 mg/50 ml) once weekly for 6 weeks then once weekly for 3 weeks at 3, 6 and 12 months.

Length of follow-up

Median follow up: 15 months

Outcome measures and effect size

Recurrence rate at 1 year follow up: 21/40 (55%) in GEM group vs 35/40 (87.5%) in BCG group, p = 0.002

Time to first recurrence, months: 3.9 months (95% CI 3.0–7.0) in GEM group vs 3.1 months (95% CI 2.2–6.0) in BCG group

Rate of radical cystectomy due to disease progression in patients with recurrent disease: 7/21 (33%) in GEM group vs 13/35 (37.5%) in BCG group, p = 0.12

Incidence of grade 2 adverse events: 12/40 (30%) in GEM group vs 13/40 (32.5%) in BCG group, p = 0.12

Incidence of grade 3 adverse events: 3/40 (7.5%) in GEM group vs 3/40 (7.5%) in BCG group, p = 0.25

Source of funding

Not reported.

Risks of bias

Selection bias: low risk
Performance bias: low risk.
Attrition bias: low risk
Detection bias: low risk

Additional comments

Study, country

Gacci, 2006
Italy

Study type, study period

Observational study.
Study period not reported.

Number of patients

19

Patient characteristics

Inclusion criteria: patients with T1G3 bladder tumour who did not respond to two 6-week courses of BCG.
Baseline characteristics:

	GEM (N = 9)	BCG (N = 10)
Male	7	8
Mean age, yrs	75	73.6
Median time from last recurrence, months	7	7
Median tumour diameter, cm	1	1.5

Intervention

Induction course: 6-week administration of gemcitabine (2,000 mg/50 ml) retained in the bladder for at least one hour. Maintenance therapy: gemcitabine as above once weekly for 3 consecutive weeks at 3, 6, 12 and 24 months.

Comparison

Induction course: 6-week administration of BCG (Tice strain, 2ml, 5 x 10^8 CFU, diluted in 50 ml) retained in the bladder for at least one

hour.
Maintenance therapy: single instillation as above at 3, 6, 12 and 24 months.

Length of follow-up

Median 20 months (GEM group: 19 months, BCG group, 20 months)

Outcome measures and effect size

Tumour recurrence after treatment:
6/9 (GEM) vs 5/10 (BCG).

Tumour progression after treatment:
2/9 (GEM) vs 4/10 (BCG)

Mean time to recurrence:
6.5 months (GEM) vs 8.2 months (BCG)

Mean time to progression:
8.5 months (GEM) vs 5.5 months (BCG)

Incidence of adverse events:
2/9 (GEM, one urinary irritation, one fever) vs 3/10 (BCG, two fever, one haematuria).

Bladder preservation rate:
7/9 (GEM) vs 6/10 (BCG)

Overall survival:
9/9 (GEM) vs 8/10 (BCG)

Source of funding

Not reported

Risks of bias

Selection bias: unclear/unknown risk. Method of allocation to treatment not reported.
Performance bias: high risk. Method for selection of controls is not reported, but it is assumed that a historical control group was used.
Attrition bias: unclear/unknown risk. Participant flow not reported.
Detection bias: unclear/unknown risk. Reliability of measurement and reporting of outcomes is not clear. Outcomes are defined in study methods, but used ambiguously in the reporting of the results.

Additional comments

Study, country

Matsumoto, 2012
Japan

Study type, study period

Observational study.
Included patients were treated between 1985 and 2008.

Number of patients

183

Patient characteristics

Inclusion criteria: Patients with diagnosed BCG-relapsing (recurrence after a previous complete response to a single induction course of BCG therapy and a disease-free period of at least 6 months) NMIBC (pTa or pT1).

Baseline characteristics:

	BCG (n = 119)	Chemo (n = 24)	None (n = 40)
Mean age at BCG relapse, yrs	66.6	67.8	69.7
Male, n (%)	100 (84)	17 (70.8)	32 (80)
Grade 1 or 2 tumour, n (%)	74 (62.2)	14 (58.3)	33 (82.5)
Grade 3 tumour, n (%)	45 (37.8)	10 (41.7)	7 (17.5)
Single tumour, n (%)	52 (43.7)	11 (45.8)	21 (52.5)
Multiple tumours, n (%)	67 (56.3)	13 (54.2)	19 (47.5)

Intervention

BCG treatment (Connaught strain 81 mg or Tokyo 172 strain 40 or 80 mg) begun 4–5 weeks after TURBT and continued weekly for 6–8 weeks.

Comparison

Patients in the 'chemo' group received MMC 30 mg or epirubicin 50 mg begun 4–5 weeks after TURBT and continued weekly for 6–8 weeks.
OR
No intravesical therapy after tumour recurrence.

Length of follow-up

Median follow up from time of BCG relapse: 5.1 years (range 0.4–15.2).

Outcome measures and effect size

Rate of subsequent tumour recurrence, hazard ratio (BCG vs chemo*): 0.41 (95% CI 0.23, 0.72) Five year recurrence free survival rates: 59.8% (BCG), 21.6% (chemo), 43.1% (no therapy)
Source of funding
Authors declared no funding sources or conflicts of interest.
Risks of bias
Selection bias: high risk. Patients allocated based on clinician preference. Low risk patients appear to have been disproportionately allocated to the 'no treatment' group. Performance bias: high risk. Included patients were treated over a long (23 year) period, during which time clinical practice is likely to have changed. Timing of recruitment of patients in each treatment group not reported. Attrition bias: unclear/unknown risk. Participant flow not reported. Detection bias: low risk.
Additional comments
*Hazard ratio for rate of subsequent occurrence has been assumed to compare BCG group vs chemotherapy group, although this is not categorically stated by the study authors.

Study, country
Prasad, 2009. United States
Study type, study period
Observational study. Patients treated between 2002 and 2007.
Number of patients
139
Patient characteristics
Included bladder cancer patients had BCG failure after an initial 6 week course of BCG therapy.
Intervention
Intravesical BCG (114 patients)
Comparison
Intravesical BCG in combination with interferon α2B (25 patients)
Length of follow-up
Median 55.6 (range 8.5 to 120) months
Outcome measures and effect size
Rate of disease recurrence: 56.8% (BCG) vs 84.6% (BCG/IFN α2B)
Source of funding
None.
Risks of bias
Selection bias: unclear/unknown risk. Patient allocation methods/baseline characteristics not reported. Performance bias: unclear/unknown risk. Attrition bias: unclear/unknown risk. Participant flow not reported. Detection bias: unclear/unknown risk. Outcomes not precisely defined.
Additional comments
Limited study information available: only published report is a conference abstract.

3.4 Managing side effects of treatment of non-muscle-invasive bladder cancer

Review question: What is the most effective intervention for bladder toxicity following radiotherapy or BCG therapy for bladder cancer?

Rationale

Radiotherapy and intravesical BCG (BCG vaccine inserted into the bladder), treatments used for high risk bladder cancer that is confined to the bladder can result in patients being cured of their cancer and with their bladder preserved but with significant side effects which can result in patients having a poor quality of life.

Irritative urinary symptoms (urinary frequency, urgency, and pain when passing urine) are usually experienced by most patients for approximately 48 hours following intravesical BCG and for some weeks after radiotherapy. However for some patients these side effects continue long-term.

The cause of long term side effects of radiotherapy to the bladder or intravesical BCG may include bladder inflammation, abnormal blood vessel development within the bladder or scarring in the bladder. Consequently the bladder may be unable to store significant quantities of urine resulting in patients passing small volumes of urine frequently and urgently during the day and night, pain passing urine and blood in urine. These symptoms can develop up to 20 years after completion of radiotherapy to the bladder.

It is expected that this review will identify effective methods to reduce the risk of long term side effects of radiotherapy to the bladder and make recommendations for the standardisation of treatment for significant long term side effects which occur as a result of radiotherapy to the bladder or intravesical BCG.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients who develop bladder toxicity following radiotherapy or BCG therapy for bladder cancer	<u>Interventions for bladder toxicity:</u> Cystectomy Isoniazid Ofloxacin Cystistat Elmiron Anticholinergics Botox Alum Formalin Embolisation Catherisation Hyperbaric oxygen Reduced dose of intravesical BCG Increased time between	Each other No intervention	• Treatment-related toxicity • Health-related quality of life inc. patient reported outcomes

	treatments of intravesical BCG		

METHODS

Information sources

A literature search was performed by the information specialists (EH and SA).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. Randomised trial and comparative studies were included when available. Non-comparative data was considered for interventions where there were no comparative studies.

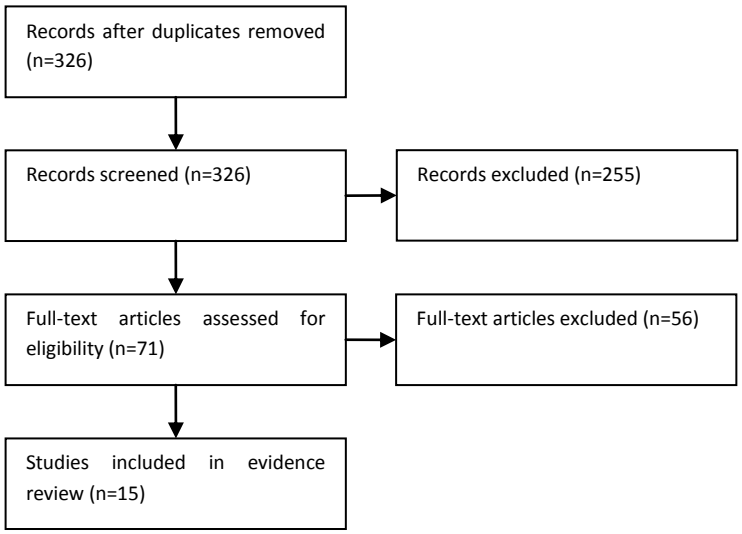
Data synthesis

Evidence was presented using GRADE. Meta-analysis was not possible for this review.

RESULTS

Result of the literature searches

Figure 56. Study flow diagram



Study quality and results

No evidence was identified for health-related quality of life across any of the interventions. No evidence was identified for the following interventions specified in the PICO: cystectomy, botox, alum, embolisation, catheterisation, increased time between treatments of BCG, elmiron. Evidence is summarised in Tables 87-93.

Evidence statements

Ofloxacin

One randomised trial (115 participants) of moderate quality was identified comparing BCG therapy plus ofloxacin with BCG therapy plus placebo in patients with superficial bladder cancer. Treatment with 2 x 200mg ofloxacin with each BCG instillation resulted in a lower rate of mild to moderate adverse events compared to placebo between instillations four and six, and a lower rate of severe adverse events between instillations one and nine. However, the proportion of participants specifically with bladder toxicity was not reported, as the outcome of adverse events included both local and systemic symptoms.

Isoniazid

Two randomised trials (997 participants) provided moderate quality evidence on the efficacy of isoniazid for the prevention of BCG-induced bladder toxicity. In both studies the 95% confidence intervals of the effect sizes (risk ratios) included the null value, so there is no strong evidence that isoniazid has an effect on the rate of chemical cystitis, frequency or haematuria (van der Meijden et al., 2001) or bladder toxicity (including haematuria, dysuria, and frequency) (Al Khalifa et al., 2000). When toxicity was sub-grouped by severity, participants receiving isoniazid were more likely to experience mild toxicity and less likely to experience severe toxicity than the placebo group. However, it should be noted that this data was based on a low number of participants.

Oxybutynin

One randomised trial (Johnson *et al.*, 2013) of 50 participants provided low quality evidence of an increase in urinary symptoms (frequency and burning) and systemic symptoms (fever, dry mouth) in those treated with oxybutynin alongside BCG treatment compared to those in the placebo group.

Reduced BCG dose

High quality evidence from one trial of reduced dose BCG reported by Brausi *et al.* (2014) stated that there were no differences between rates of local and systemic BCG side effects between the 1/3 dose BCG group and the full-dose BCG group (RR 0.95, 95% CI 0.86 to 1.06). Reducing the dose of BCG did not decrease the percentage of patients who discontinued treatment due to side effects.

Formalin

Two case series studies (12 participants) reported the effects of intravesical formalin for treating bladder haemorrhage secondary to radiation-induced cystitis. Both studies reported that all patients had a good response to treatment with cessation of bleeding observed for three to five months (very low quality evidence).

Hyperbaric oxygen therapy (HBOT)

Seven case series studies (153 participants) provided very low quality evidence on the efficacy of HBOT for treating radiation-induced cystitis. Overall 94/153 (61%) participants showed a complete resolution of haematuria, with effectiveness ranging from 27% to 100% across studies. In most studies patients had received previous treatment for cystitis, such as alum or formalin, without success.

Sodium hyaluronate

One case series (54 patients) provided very low quality evidence on the efficacy of intravesical sodium hyaluronate for the treatment of chemical-induced cystitis in bladder cancer patients treated with Mitomycin C or BCG therapy. It is not stated whether Cystistat was the treatment used. Bladder capacity increased in all patients after treatment (mean difference 226.1 ml, 95% CI 207.1 to 245 ml). Patient-reported pain as measured by the Visual Analogue Scale (VAS) decreased in all patients (mean difference -7.7, 95% CI -8.12 to -7.31). VAS scores range from 1 to 10, with 10 indicating maximum pain tolerated.

Table 87. GRADE evidence profile: Ofloxacin for the prevention of BCG-induced toxicity in superficial bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ofloxacin	Control	Relative (95% CI)	Absolute	
Toxicity: At least one Class I or II adverse event (follow-up between instillations 4 and 6; assessed with: Self-recorded by patient (classified by investigator criteria))											
1[1]	randomised trial	none	none	serious[2]	none[3]	none	41/54 (75.9%)	51/54 (94.4%)	RR 0.80 (0.68 to 0.95)	189 fewer per 1000 (from 47 fewer to 302 fewer)	⊕⊕OO LOW
Toxicity: At least one Class III adverse event (follow-up between instillations 1 and 9; assessed with: Self-recorded by patient (classified by investigator criteria))											
1[1]	randomised trial	none	none	serious[2]	none[3]	none	31/57 (54.4%)	44/58 (75.9%)	RR 0.72 (0.54 to 0.95)	212 fewer per 1000 (from 38 fewer to 349 fewer)	⊕⊕OO LOW
Health-related quality of life											
0	no evidence available										

[1] Colombel (2006). BCG+ofloxacin versus BCG+placebo
[2] Outcome of toxicity includes both local adverse events and systemic adverse events such as fever, myalgia, and fatigue, which limits the directness of this outcome to the review question
[3] Small sample size and low number of events limits precision of outcome

Table 88. GRADE evidence profile: Isoniazid for the prevention of BCG-induced bladder toxicity in superficial bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isoniazid	Control	Relative (95% CI)	Absolute	
Bladder toxicity: Chemical cystitis (follow-up 12-18 months; assessed with: Patient report (Irritative bladder symptoms with negative urine culture))											
1[1]	randomised trial	none	none	none	serious[2]	none	113/256 (44.1%)	111/263 (42.2%)	RR 1.05 (0.86 to 1.27)	20 more per 1000 (from 59 fewer to 114 more)	⊕⊕⊕O MODERATE
Bladder toxicity: Frequency (follow-up 12-18 months; assessed with: Patient report)											
1[1]	randomised trial	none	none	none	serious[2]	none	144/256 (56.3%)	142/263 (54%)	RR 1.04 (0.89 to 1.22)	22 more per 1000 (from 59 fewer to 119 more)	⊕⊕⊕O MODERATE
Bladder toxicity: Macroscopic haematuria (follow-up 12-18 months; assessed with: Not specified)											
1[1]	randomised trial	none	none	none	serious[2]	none	78/256 (30.5%)	93/263 (35.4%)	RR 0.86 (0.67 to 1.1)	50 fewer per 1000 (from 117 fewer to 35 more)	⊕⊕⊕O MODERATE
Bladder toxicity (haematuria, dysuria, frequency) (follow-up 2 years; assessed with: Recorded by investigators)											
1[3]	randomised trial	none	none	none	serious[2]	none	28/80 (35%)	38/80 (47.5%)	RR 0.74 (0.51 to 1.07)	123 fewer per 1000 (from 233 fewer to 33 more)	⊕⊕⊕O MODERATE
Mild bladder toxicity (sub-group) (follow-up 2 years; assessed with: Recorded by investigators)											
1[3]	randomised trial	none	none	none	serious[4]	none	14/28 (50%)	5/38 (13.2%)	RR 3.80 (1.55 to 9.32)	368 more per 1000 (from 72 more to 1000 more)	⊕⊕⊕O MODERATE
Moderate bladder toxicity (sub-group) (follow-up 2 years; assessed with: Recorded by investigators)											
1[3]	randomised trial	none	none	none	serious[4]	none	7/28 (25%)	8/38 (21.1%)	RR 1.19 (0.49 to 2.89)	40 more per 1000 (from 107 fewer to 398 more)	⊕⊕⊕O MODERATE
Severe bladder toxicity (sub-group) (follow-up 2 years; assessed with: Recorded by investigators)											
1[3]	randomised trial	none	none	none	serious[4]	none	7/28 (25%)	25/38 (65.8%)	RR 0.38 (0.19 to 0.75)	408 fewer per 1000 (from 164 fewer to 533 fewer)	⊕⊕⊕O MODERATE
Health-related quality of life											
0	no evidence available										

[1] van der Meijden (2001). BCG+isoniazid versus BCG alone
[2] Wide confidence intervals and/or low number of events reduces the precision of this outcome
[3] Al Khalifa (2000). BCG+isoniazid versus BCG+placebo
[4] Low number of participants and events reduces the precision of this outcome

Table 89. GRADE evidence profile: Oxybutynin for the prevention of BCG-induced toxicity in superficial bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oxybutynin**	**Placebo**	**Relative (95% CI)**	**Absolute**	
Urinary symptoms											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	25	25	[4]	-	⊕⊕OO LOW
Systemic symptoms											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	25	25	[5]	-	⊕⊕OO LOW
Health-related quality of life											
0	No evidence available										

[1] Johnson 2013
[2] Method of randomisation and allocation concealment not reported.
[3] Small sample size (n=50). Number of events not reported.
[4] Treatment group had greater increase in urinary frequency (p=0.004) and burning on urination compared to placebo (p=0.04). No significant differences in other urinary symptoms.
[5] Treatment group reported increases in fever (p<0.0001), flu-like symptoms (p=0.0008), dry mouth (p=0.045) and constipation (p=0.001) compared to placebo.

Table 90. GRADE evidence profile: Reduced BCG dose for BCG-induced toxicity: 1/3 dose versus standard dose

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Reduced dose BCG**	**Standard dose BCG**	**Relative (95% CI)**	**Absolute**	
Bladder toxicity (assessed with: Local or systemic side-effects (1-yr treatment))											
1[1]	randomised trials	none	none	none	none	none	221/334 (66.2%)	228/329 (69.3%)	RR 0.95 (0.86 to 1.06)	35 fewer per 1000 (from 97 fewer to 42 more)	⊕⊕⊕⊕ HIGH
Health-related quality of life											
0	No evidence available					none	-	-	-	-	

[1] Brausi 2014

Table 91. GRADE evidence profile: Formalin for the treatment of bladder haemorrhage secondary to radiation-induced cystitis

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Formalin	Control	Relative (95% CI)	Absolute	
Bladder toxicity (follow-up 3-5 months; assessed with: Cessation of bleeding)											
2[1]	observational studies[2]	none	none	serious[3]	serious[4]	none	12/12 (100%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	no evidence available					none	-	-	-	-	

[1] Likourinas (1979); Kumar (1975)
[2] Case series
[3] No information provided about cancer site, stage or grade in patients with radiation-induced bladder haemorrhage. Possibly non-bladder cancer patients. No details provided about radiation therapy received.
[4] Small number of studies and participants limits the precision of this outcome

Table 92. GRADE evidence profile: Hyperbaric oxygen therapy (HBOT) for the treatment of radiation-induced hemorrhagic cystitis

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBOT	Control	Relative (95% CI)	Absolute	
Bladder toxicity (follow-up 4 to 102 months; assessed with: resolution of haematuria)											
7[1]	observational studies[2]	none	serious[3]	serious[4]	none	none	94/153 (61.4%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	no evidence available					none	-	-	-	-	

[1] Del Pizzo (1998); Matthews (1999); Corman (2003); Parra (2011); Weiss (1994); Rijkmans (1989); Lee (1994)
[2] Case series
[3] Effectiveness ranged from 27% to 100% across studies
[4] All studies included participants with prostate cancer and/or gynaecological cancers which limits the directness of the evidence to the population specified in the PICO

Table 93. GRADE evidence profile: Sodium hyaluronate for the treatment of chemical-induced cystitis

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium hyaluronate	Control	Relative (95% CI)	Absolute	
Bladder capacity (millilitres) (follow-up 8 weeks; measured with: patient reported diary - mean of urinary volumes for at least 2 days; Better indicated by higher values)											
1[1]	observational studies[2]	none	none	serious[3]	none	none	54	-	Mean difference 226.1 (207.1 to 245)	-	⊕OOO VERY LOW
Pain (follow-up 8 weeks; measured with: Visual Analogue Scale (VAS); range of scores: 1-10; Better indicated by lower values)											
1[1]	observational studies[2]	none	none	serious[3]	none	none	54	-	Mean difference -7.7 (-8.12 to -7.31)	-	⊕OOO VERY LOW
Health-related quality of life											
0	no evidence available					-	-	-	-	-	

[1] Sommariva (2010)
[2] Case series
[3] Out of 54 participants, 30 had received treatment with Mitomycin C and 24 had received intravesical BCG therapy, which limits the directness of the evidence to the population specified in the PICO

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Reason: expert review/commentary

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Reason: not relevant to PICO

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Evidence tables

Prevention of BCG toxicity

Reference, study design, country	Sample size, M/F (%) Age (range)	Tumour type Stage/Grade (%)	BCG regimes	Follow-up Median/mean (range)	Results	Comments
Colombel (2006) RCT France	115 M 87% / F 13% Mean = 66 (range ns)	pTa (35%); pT1 (52%); CIS (13%); Grade 1 (8%); Grade 2 (20%); Grade 3 (72%)	BCG (ImmunuCyst, 81mg Connaught strain) plus ofloxacin (2x200mg) versus BCG plus placebo BCG given 1x/week for 6 wks, then after 6 wks drug-free a 2nd round of 3 weekly instillations.	Minimum of 1year follow-up	At least one Class II or III adverse event: 39% (n=41) ofloxacin; 95% (n=51) placebo At least one Class III adverse event: 54% (n=31) ofloxacin; 76% (n=44) placebo	Class I =mild adverse event Class III = severe adverse event
Van der Meijden (2001) Randomised trial EORTC multicentre	957 randomised; 837 eligible for analysis M 77% / F 20% Median 66 (27 -87)	Ta (62%); T1 (35%) Grade 1 (37%); Grade 2 (48%); Grade 3 (12%)	BCG (Tice-strain) $5x10^8$ colony forming units weekly for 6 wks, 7- 15 days after TUR; BCG plus 900mg isoniazid (300mg orally the day before, same day and day after instillation) 50mg epirubicin Initial treatment was followed by 3 weekly instillations at months 3,6, 12, 18, 24, 20, and 36	3.5 years (for recurrence)	Chemical cystitis: 31% (n=82) epirubicin; 42% (n=111) BCG only; 44% (n=113) BCG plus isoniazid Frequency: 42% (n=11) epirubicin; 54% (n=142) BCG only; 56% (n=144) BCG plus isoniazid Macrospcopic haematuria: 17% (n=45) epirubicin; 35% (n=93) BCG only; 30% (n=78) BCG plus isoniazid	Non-blinded and no placebo control
Al Khalifa (2000) Randomised trial Sweden	172 recruited; 160 analysed M 85% / F 15% Mean 73 years	All pTa-T1, pTis, G1-G3 Numbers not reported	BCG (81mg, 1-3 weeks after TUR, 1x/week for 6 weeks) plus prophylactic isoniazid or placebo. 900mg isoniazid (300 mg taken when BCG was emptied, the second and third (both 300mg) in the mornings of the following 2 days, for all six treatments)	2 years	Local side-effects (dysuria, increased micturation, haematuria): 35% (n=28) BCG plus isoniazid; 48% (n=38) BCG plus placebo	
Johnson (2013) Randomised trial USA	50 BCG naive patients 82% Male, 18% female Mean age 67	All Cis, Ta or T1. Numbers not reported	10mg Oxybutynin ER (n=25): 1 tablet daily, beginning the night before first intravesical treatment and throughout 6 weeks of treatment. Identical placebo (n=25)	Follow-up over 6 week treatment	Urinary frequency: greater increase with treatment versus control on the evening after treatment. (p=0.004). Burning on urination: greater increase with treatment versus control on the evening after treatment. (p=0.04). No differences for urinary urgency, bladder pain, spasm or haematuria. Fever: more common in treatment than placebo group (p<0.0001) Arthralgia: no changes between 2 groups (p=0.32) Constipation: more common in treatment group (p=0.001). Dry mouth: increase in treatment group compared to control (p=0.045)	Blinded study. Details of BCG treatment not provided. Method of randomisation not reported. Number of events in each group not reported.

Reduced dose BCG

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Included studies
Brausi 2014	Randomised trial 1997 to 2005	1316 who started BCG Median age 68 (29 to 85) 81% M/ 18% F	Patients with resected pT1G3 or multiple pTa-T1 Grade 1-3 tumours of bladder.	BCG: One-third dose with 1yr maintenance, vs. One-third dose with 3yr maintenance, vs. Full-dose-1yr maintenance, vs. Full-dose-3-yr maintenance OncoTICE strain $5x10^8$ CFU. 1/3 dose dissolved in saline. Patients randomised within 14 days of TUR. Isoniazide given for fever, BCG cystitis, allergic reactions, severe illness and BCG sepsis	4 trial arms compared with each other	NR	**Toxicity** 826 (62.8%) reported local side effects, 403 (30.6%) systemic side effects, 914 (69.5% reported local or systemic side effects. The percentage of patients with at least one side effect was similar in the 4 treatment arms (p=0.41), both overall and in the different time period. Most frequent side effects: chemical cystitis 35%, general malaise 15.5%. Neither reducing the dose nor shortening the duration of maintenance decreased the number of patients who discontinued treatment due to side-effects.	Intent-to-treat analysis performed. Efficacy of BCG treatment reported in separate paper.

Hyperbaric oxygen therapy (HBOT) for radiation-induced hemorrhagic cystitis

Reference, study design, country	Sample size, M/F (%) Age (range)	Tumour type Stage/Grade (%)	Toxicity	Intervention	Radiation received	Follow-up Median/mean(range)	Results	Comments
Del Pizzo (1998) Case series USA	11 M 45% / F 55% Mean age 62 (46-74)	4 prostate; 4 uterine; 2 cervical; 1 bladder cancer Stage/grade ns	Recurrent intractable haematuria Confirmed by cystoscopy and biopsy.	HBOT: 100% O_2 at a pressure of 2.0 atm for 90 mins, 5 days/week. Average no. of treatments 40 (range 28 to 64)	EBRT mean dosage 7,500 cGy (range 6,000 to 9,600). Mean time from EBRT to symptoms 7 years (range 16 months to 12 years)	71 months	3 (27%) had long term resolution of symptoms. At 2.5yr follow-up 8 were asymptomatic, 3 had urinary diversion. After 5 yrs 5/8 had recurrence requiring diversion and 2 of those 5 had subsequent cystectomy	All received previous treatment with catheter irrigation, alum, silver nitrate and/or formalin without success before HBOT
Matthews (1999) Case series USA	17 M 82% / F 18% Mean age 62 (49-86)	11 prostate; 3 bladder; 1 endometrial; 1 cervical; 1 rectal cancer Stage/grade ns	All patients had undergone treatment to control haematuria.	HBOT: 2 to 2.5 atm for 90 mins daily 5 days/week until haematuria controlled	Mean dosage 6,600cGy. Time from radiation to symptoms range 2 to 180 months	21 months (9 to 60)	11 (64%) completely resolved haematuria with cystoscopy showing normal bladder mucosa and no recurrence at follow-up. 2 (11%) had residual microscopic haematuria; 2 (11%) had continued gross	Bladder irrigation (7); fulguration in all; alum (2); aminocaproic acid (2) No HBOT complications reported

Reference, study design, country	Sample size, M/F (%) Age (range)	Tumour type Stage/Grade (%)	Toxicity	Intervention	Radiation received	Follow-up Median/mean(range)	Results	Comments
							haematuria despite improvement in bleeding frequency and quantity	
Corman (2003) Case series USA	62 (57 analysed) M 90% / F 10% Mean age 70 (15-88)	82% prostate; 10% bladder cancer Stage/grade ns	Hemorrhagic cystitis confirmed by cystoscopy	HBOT: 100% O_2 at 2.4 atm for 90 mins daily 5 to 7 days/week. Average 33 treatments (range 9 to 68)	Mean time from radiation to symptoms 48 months (range 0 to 335)	Range 10 to 120 months	21 (34%) completely resolved haematuria; 28 (45%) showed marked improvement; 6 (10%) unchanged; 2 (3%) worsened 6 of those who showed improvement had recurrent symptoms and were re-treated with HBOT, in 4/6 symptoms improved.	7 patients ended HBOT early due to medical co-morbidities (4); claustrophobia (2); temporary resolution of symptoms (1)
Parra (2011) Case series Chile	25 M 84% / F 16% Mean age 67 (42-80)	20 prostate; 1 bladder; 3 cervical; 1 endometrial	Hemorrhagic cystitis confirmed by cystoscopy. HBOT considered after failure of treatments including cauterization	HBOT: 100% O_2 at 2.2 atm for 90 mins. Average 40 sessions (range 15-44)	Mean time from radiation to symptoms 31 months (range 1 to 106)	21 months (3 to 66)	All patients responded to HBOT with progressive and complete disappearance of macroscopic bleeding. 1 patient had haemorrhage in session 29, requiring KTP laser coagulation. No hospitalisation due to bleeding required for any patient	2 cases of barotraumatic otitis which were both treated with good response
Weiss (1994) Case series USA	13 Gender ns Mean age 69 (43-82)	5 uterine; 6 prostate; 2 bladder cancer	Radiation-induced cystitis. All had received previous unsuccessful treatment with formalin, fulguration, or alum	HBOT: 100% O_2 at 2.0 atm for 120 mins daily over 60 consecutive days	4,000cGy to 6,975cGy	30 months (4 months to 8.5 years)	12/13 (92%) haematuria resolved after an average of 33 treatments. One patient required cystectomy and urinary diversion despite 47 HBOT treatments.	Minimal side effects reported
Rijkmans (1989) Case series Netherlands	10 M 100% Mean age 71 (61-83)	8 bladder; 2 prostate cancer	Radiation-induced cystitis. All had severe macroscopic haematuria resistant to current therapy	HBOT: 20 sessions (3 patients received 40 sessions) of 100% O_2 at 3 bar pressure for 90 mins. 5 or 6 times a week.	60Gy. Interval between RT and onset of haematuria varied from 6 months to 3 years	Range 2-24 months	6/10 (60%) macroscopic haematuria stopped completely. Haematuria decreased in the other 4 patients (all with recurrent or residual bladder malignancies)	
Lee (1994) Case series Taiwan	20 F 100% Mean age 63 (42-79)	19 cervical; 1 bladder cancer	Haemorrhagic radiation cystitis. Previous treatment including intravesical irrigation, antibiotics, and tranexamic acid had all failed.	HBOT: 100% O_2 at 2.5 atm, for 100 min once a day, 6 days/week.	6200 cGy. Haematuria onset average 9.5years after RT	Mean (range)= 14 months (5-41)	After an average of 44 HBOT sessions (range 10-87 sessions), haematuria was completely halted in 16 patients (80%) and markedly decreased in 2 patients (10%). Cystoscopy showed decrease in hemorrhagic sites and telangiectasis of the bladder mucosa.	One patient had urinary frequency and urgency without haematuria during treatment. One patient failed to respond to HBOT and underwent ileal conduit diversion

Intravesical formalin for radiation-induced hemorrhagic cystitis

Reference, study design, country	Sample size, M/F (%) Age (range)	Tumour type Stage/Grade (%)	Toxicity	Intervention	Radiation received	Follow-up Median (range)	Results	Comments
Likourinas (1979) Case series Greece	17 (6 with radiation cystitis) M 82% / F 18% Age range 64-80 years	Not reported	Haemorrhage due to radiation cystitis. Prior to formalin, cystoscopic fulguration continuous irrigation, epsilon aminocaproic acid and hypertronic glucose used in an effort to control bleeding	Obvious bleeding points controlled by fulguration. Intravesical formalin instillation with general or spinal anaesthesia. 100-150ml of 10% formalin inserted into bladder at 15cm pressure. Traction applied to catheter during infusion to avoid leakage of formalin into posterior urethra. Catheter clamped for 15minutes, allowed to drain, and then irrigated with normal saline. Catheter removed after 6 days.	Not reported	Unclear	100% of radiation cystitis (n=6) classified as 'very good' control of bleeding, mostly after 1 instillation. Bleeding ceased within 12-24 hrs for 4-5 months. 16 patients developed tachycardia lasting for 2 hours after instillation. One patient developed UTI.	
Kumar (1975) Case series USA	10 (6 with radiation cystitis) M 50% / F 50% Age range 10-74 years	Not reported	Intractable haematuria secondary to radiation cystitis	Obvious bleeding points controlled by fulguration. Intravesical formalin instillation with general or spinal anaesthesia. 10-30cc of 10% formalin inserted into bladder at 15cm pressure. Catheter clamped for 15minutes, allowed to drain, but the bladder was not irrigated. Catheter was removed in 1 to 8 days.	Not reported	Unclear	100% of radiation cystitis (n=6) showed almost complete or complete control of bleeding within 24-48 hours, for at least 3 months, mostly after 1 instillation (1 patient required a repeat instillation). Fever, atelectasis and lower extremity phlebitis were post-operative complications probably not specifically related to formalin.	

Sodium hyaluronate for chemical-induced cystitis

Reference, study design, country	Sample size, M/F (%) Age (range)	Tumour type Stage/Grade (%)	Toxicity	Intervention	Radiation/ chemo received	Follow-up Median (range)	Results	Comments
Sommariva (2010) Case series Italy	69 M 100% 54-81 years	24 BCG therapy: 13 pT1, 11 pTa, G2-3 12 MMC 40mg + hyperthermia: 4 pT1 G2-3, 7 pTa, 1 Cis	Iatrogenic acute cystitis. Almost all patients complained of frequency with urgency, with or without burning and/or	Intravesical instillations of sodium hyaluronate, 40 mg diluted in 50 mL, held in bladder for 1 hour, weekly for 8 to 24 weeks, depending on how symptoms released. In the first 4 weeks dexamethasone 32 mg was mixed in for its topical anti-inflammatory action and good mucosal penetration. To allow	Weekly BCG therapy. Cystitis symptoms after 3rd or 4th dose.	Outcomes measured before and after treatment (8 weeks)	After 4 weeks BC increased in all patients, and urgency and pain decreased. Mean BC increased from 58.4 to 283.7 mL (mean difference 226.1 ml, 95% CI 207.1 to 245 ml). VAS score dropped from 8.6 to 0.9 at the end of treatment (mean difference -7.7, 95% CI -8.12 to	2 treatment failures were due to a inability to keep drugs in bladder for >10mins. No adverse reactions were observed related to the catheters or

Reference, study design, country	Sample size, M/F (%) Age (range)	Tumour type Stage/Grade (%)	Toxicity	Intervention	Radiation/ chemo received	Follow-up Median (range)	Results	Comments
		18 MMC 40mg: 9 relapsing G1-2 and/or multifocal pTa, 7 pT1, 2 pTaG3 who did not tolerate BCG and refused cystectomy	suprapubic pain that got worse as bladder filled. 10 also had urge-incontinence	patients with marked overactive bladder to keep these drugs within the bladder, lidocaine 2% 30 ml was instilled 30 minutes before treatment. When symptoms were particularly acute oral analgesics and antispastics were also provided, and if necessary the penis was clamped to keep the solution in the bladder. Treatment was continued, for another 4 weeks, even in patients with total remission of symptoms to prevent recurrence.			-7.31).	drugs used. Patients with non-invasive bladder tumours were able to restart their cancer therapy. (15 patients with cystitis after RT for prostate cancer not included as results were reported separately)

3.5 Follow-up after treatment for non-muscle-invasive bladder cancer

Review question: What are the optimal follow-up protocols for low/intermediate risk and high-risk non-muscle invasive bladder cancer?

Rationale

Currently all patients with NMIBC require regular cystoscopic surveillance of their bladder and high risk patients may require additional imaging to look for progression. Long term cystoscopic surveillance is expensive and may not be necessary in low risk cases.

Although there is general agreement that NMIBC patients require cystoscopic surveillance to detect recurrence, there are variations in frequency and length of follow-up. The optimal tests for detecting progression are unknown. It is also difficult to co-ordinate current surveillance protocols with concurrent treatment e.g. with intravesical therapy.

Cystoscopic surveillance could be rationalised into low, intermediate and high risk group. Defining the optimal length of follow-up in low risk patients would allow many to be safely discharged whilst high risk patients would benefit from an integrated follow-up that is synchronised with treatment and includes imaging for progression.

Alternative approaches could include non invasive follow up using ultrasound for some risk groups and/or defining a group of patients in whom invasive surveillance may not be appropriate.

Patients with NMIBC are at increased risk of developing upper tract TCC. Tests to detect upper tracts tumour in these patients are variably performed at present but should be considered within follow up protocols

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients who have undergone curative treatment for NMIBC Subgroups: - Low/ intermediate-risk NMIBC - High-risk NMIBC	Follow up: Cystoscopy intervals (rigid/flexi) Intravenous urography (IVU) CT Ultrasound Urine tests (Cytology, NMP22, UroVysion, ImmunoCyt)	No follow-up Each other (including frequency and duration of follow-up)	• Recurrence • Overall survival • Disease progression • Disease-specific survival • Treatment related complications • Health-related quality of life • Patient experience • Patient preference

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO.

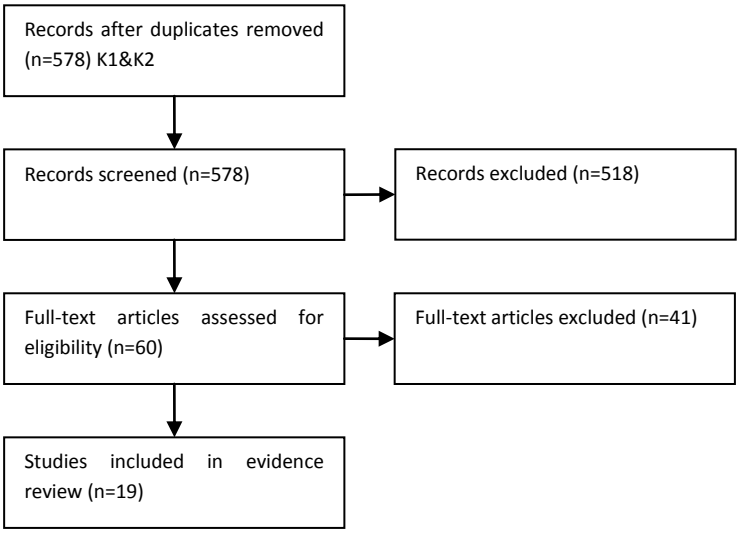
Data synthesis

One randomised trial was identified. No other comparative data was found. Therefore, data is presented from observational studies about recurrence rates during follow-up for non-muscle invasive bladder cancer. No meta-analysis was possible for this review.

RESULTS

Result of the literature searches

Figure 57. Study flow diagram



Study quality and results

Evidence is summarised in Tables 94-96.

Evidence statements

Moderate quality evidence from one randomised trial of 97 patients (Olsen *et al.*, 1995) suggests uncertainty over whether follow up frequency of three months is more or less effective than follow up with a frequency of six months in terms of recurrence, progression or overall survival.

Low quality evidence from five observational studies of patients with low-grade superficial bladder cancer report recurrence rates over long-term follow-up. Two studies including 470 patients suggest that tumour detection at the first follow-up cystoscopy is associated with a greater risk of recurrence during subsequent follow-up compared to those who are tumour-free at the first cystoscopy (Holmang *et al.*, 2002; Mariappan & Smith, 2005). All studies report a reduction in the risk of recurrence over time. Some studies suggest the risk of recurrences is greatly reduced after a tumour-free period of five years or more (Mariappan & Smith, 2005; Zieger *et al.*, 2000). In Mariappan & Smith (2005) only one (0.9%) patient had a first recurrence after being tumour-free for

five years, whereas LeBlanc *et al.* (1999) reports recurrence rates of approximately 30% in patients after remaining tumour-free for two to ten years. Another study reports that of 20 primary Ta-T1 patients who were tumour-free for five years, seven (35%) had muscle-invasive disease (Thompson *et al.*, 1993).

One retrospective observational study of 542 intermediate-high risk patients who had received BCG treatment reports that 338/542 (62%) patients were not tumour-free for five years or more. 22/204 (10.8%) patients had a recurrence after being tumour-free for five years or more (Holmang *et al.*, 2012). During the first five-years after BCG, 57 patients (10.5%) died from bladder cancer and between years six and 25, 32 patients (5.9%) died from bladder cancer.

Five observational studies report rates of upper urinary tract (UUT) recurrence ranging between 2.6% and 5.5%. Median times to UUT recurrence vary from 22 to 33 months in three studies (Miyake *et al.*, 2005; Canales *et al.*, 2006; Holmang *et al.*, 1998) and one study (Hession *et al.*, 1999) reports a mean time to recurrence of 78 months. In one study, two out of 18 UUT cancers were diagnosed by routine intravenous urography, and the other 18 presented with symptoms suggesting UUT recurrence before IVU (Miyake *et al.*, 2006). Holmang *et al.* (1998) reported that IVU performed 0 to ten months before the UUT cancer was diagnosed failed to raise suspicion of a tumour in eight out of 16 patients (including three patients with initial muscle-invasive bladder cancer).

Two studies provide low quality evidence of the accuracy of ultrasound compared with cystoscopy for the detection of recurrent tumours in patients with superficial bladder cancer. In one study, three tumours detected by cystoscopy were missed by ultrasound (Stamatiou *et al.*, 2011, and in the second study 15 patients with recurrence were not detected by ultrasound (Vallencien *et al.*, 1986).

Low quality evidence for health-related quality of life is provided by three studies (503 patients) which report that most patients experience minimal pain (Yossepowitch *et al.*, 2007) from undergoing cystoscopic follow-up, although the introduction of the cystoscope is rated as the most painful part of the procedure (van der Aa *et al.*, 2008). Waiting for test results is rated as the most distressing part of follow-up by urine testing (van der Aa *et al.*, 2008).

Table 94. GRADE evidence profile: Frequent versus less frequent follow-up for TaG1-2 bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frequent follow-up	Less frequent	Relative (95% CI)	Absolute	
Recurrence (follow-up 14.7 to 39.1 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	28/45 (62.2%)	26/52 (50%)	RR 1.24 (0.87 to 1.77)	120 more per 1000 (from 65 fewer to 385 more)	⊕⊕⊕O MODERATE
Progression (follow-up 14.7 to 39.1 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	3/45 (6.7%)	1/52 (1.9%)	RR 3.47 (0.37 to 32.17)	48 more per 1000 (from 12 fewer to 599 more)	⊕⊕⊕O MODERATE
Disease-specific mortality rate (follow-up 14.7 to 39.1 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	0/45 (0%)	0/52 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Overall mortality rate (follow-up 14.7 to 39.1 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	5/45 (11.1%)	2/52 (3.8%)	RR 2.89 (0.59 to 14.17)	73 more per 1000 (from 16 fewer to 507 more)	⊕⊕⊕O MODERATE
Treatment-related complications											
0	No evidence available										
Health-related quality of life											
0	No evidence available										
Patient experience/preference											
0	No evidence available										

[1] Olsen 1995

[2] Small number of events / confidence interval includes null value

Table 95. GRADE evidence profile: Follow-up for non-muscle invasive bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Follow-up	Control	Relative (95% CI)	Absolute	
Recurrence											
5[1]	observational studies	none	none	none	none	none	619/1125 (55%)	NA	-	-	⊕⊕OO LOW
Progression (assessed with: Progression in stage or grade)											
6[2]	observational studies	none	none	none	none	none	157/962 (16.3%)	NA	-	-	⊕⊕OO LOW
Recurrence (Upper Urinary Tract)											
5[3]	observational studies	none	none	none	none	none	102/2360 (4.3%)	NA	-	-	⊕⊕OO LOW
Overall mortality rate (Intermediate/high risk NMIBC) (follow-up 5 to 25 years)											
1[4]	observational studies	none	none	none	none	none	335/542 (61.8%)	NA	-	-	⊕⊕OO LOW
Disease-specific mortality (Ta NMIBC) (follow-up mean 84 months)											
1[5]	observational studies	none	none	none	none	none	23/217 (10.6%)	NA	-	-	⊕⊕OO LOW
Disease-specific mortality (Intermediate/high risk NMIBC) (follow-up 5 to 25 years)											
1[4]	observational studies	none	none	none	none	none	89/542 (16.4%)	NA	-	-	⊕⊕OO LOW
Treatment-related complications											
0	No evidence available										
Health-related quality of life											
0	No evidence available										
Patient experience/preference											
3[6]	observational studies	none	none	none	none	none	503	-	See Table 81		⊕⊕OO LOW

[1] Mariappan 2005; LeBlanc 1999; Zieger 2000; Oge 2000; Holmang 2012
[2] Mariappan 2005; LeBlanc 1999; Zieger 2000; Oge 2000; Thompson 1993; Holmang 2012
[3] Miyake 2006; Holmang 1998; Hession 1999; Canales 2006; Sternberg 2013
[4] Holmang 2012
[5] Zieger 2000
[6] Yossepowitch 2007; Van der Aa 2008; Vriesema 2000

Table 96. Patient experience and preference for follow-up of NMIBC

Study	Patients	Results
Yossepowitch 2007	200 NMIBC undergoing flexi cystoscopy follow-up	**Pain:** 74% reported minimal or no pain. Higher pain ratings from those undergoing fulguration compared to those undergoing cystoscopy alone.
Van der Aa 2008	201 NMIBC undergoing 3-monthly flexible cystoscopy and urinal microsatellite analysis	**Discomfort:** introduction of the cystoscope was most uncomfortable and painful part of cystoscopy and awaiting the result was the most distressing time of urine test.
Vriesema 2000	102 NMIBC undergoing flexi cystoscopy follow-up	**Bothersome:** Not bothersome 29/85 (34%); somewhat bothersome 45/85 (53%); very bothersome 11/85 (13%). No differences in ratings by age or gender.

References to included studies

Aa, MN et al. Patients' perceived burden of cystoscopic and urinary surveillance of bladder cancer: a randomized comparison. BJU International 2008; 101: 1106-1110.

Canales, BK et al. Risk factors for upper tract recurrence in patients undergoing long-term surveillance for stage ta bladder cancer. Journal of Urology 2006; 175(1): 74-77.

Hession, P et al. Intravenous urography in urinary tract surveillance in carcinoma of the bladder. Clinical Radiology 1999; 54(7): 465-467.

Holmang, S and Johansson, SL. Stage Ta-T1 bladder cancer: the relationship between findings at first followup cystoscopy and subsequent recurrence and progression. Journal of Urology 2002; 167(4): 1634-1637.

Holmang, S and Strock, V. Should follow-up cystoscopy in bacillus Calmette-Guerin-treated patients continue after five tumour-free years? European Urology 2012; 61(3): 503-507.

Holmang, S et al. Long-term followup of a bladder carcinoma cohort: routine followup urography is not necessary. Journal of Urology 1998; 160(1): 45-48.

Leblanc, B et al. Long-term followup of initial Ta grade 1 transitional cell carcinoma of the bladder. Journal of Urology 1999; 162(6): 1946-1950.

Mariappan, P and Smith, G. A similar surveillance schedule for G2Ta and G1Ta bladder tumours permits safe discharge at 5 years: results of a 25-year prospective database. BJU International 2005; 95: 53-53.

Mariappan, P and Smith, G. A surveillance schedule for G1Ta bladder cancer allowing efficient use of check cystoscopy and safe discharge at 5 years based on a 25-year prospective database. Journal of Urology 2005; 173(4): 1108-1111.

Miyake, H et al. Limited significance of routine excretory urography in the follow-up of patients with superficial bladder cancer after transurethral resection. BJU International 2006; 97(4): 720-723.

Oge, O et al. Proposal for changes in cystoscopic follow-up of patients with low-grade pTa bladder tumor. European Urology 2000; 37(3): 271-274.

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Stamatiou, K et al. Accuracy of modern ultrasonographic techniques in the follow up of patients with superficial bladder carcinoma. Medical Ultrasonography 2011; 13(2): 114-119.

Sternberg, IA et al. Upper tract imaging surveillance is not effective in diagnosing upper tract recurrence in patients followed for nonmuscle invasive bladder cancer. Journal of Urology 2013; 190(4): 1187-1191.

Thompson, RA, Jr. et al. Late invasive recurrence despite long-term surveillance for superficial bladder cancer. Journal of Urology 1993; 149(5): 1010-1011.

Vallancien, G et al. Can transabdominal ultrasonography of the bladder replace cystoscopy in the followup of superficial bladder tumors? Journal of Urology 1986; 136(1): 32-34.

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Yossepowitch, O, Herr, HW, and Donat, SM. Use of urinary biomarkers for bladder cancer surveillance: patient perspectives. Journal of Urology 2007; 177(4): 1277-1282.

Zieger, K et al. Long-term follow-up of noninvasive bladder tumours (stage Ta): recurrence and progression. BJU International 2000; 85(7): 824-828.

References to excluded studies (with reasons for exclusion)

Hernandez, V et al. Safety of active surveillance program for recurrent nonmuscle-invasive bladder carcinoma. Urology 2009; 73(6): 1306-1310.

Reason: not relevant to PICO – active surveillance

Anastasiadis, A et al. Follow-up procedures for non-muscle-invasive bladder cancer: an update. Expert Review of Anticancer Therapy 2012; 12(9): 1229-1241.

Reason: expert review

Ceylan, K et al. Comparison of cystoscopy with diffusion-weighted magnetic resonance images used in the diagnosis and follow-up of patients with bladder tumors. Asian Pacific Journal of Cancer Prevention: Apjcp 2010; 11(4): 1001-1004.

Reason: population not relevant – non follow-up patients

David, KA et al. Surveillance of urothelial carcinoma: stage and grade migration, 1993-2005 and survival trends, 1993-2000. Cancer 2009; 115(7): 1435-1447.

Reason: not relevant to PICO

Forsyth, I, Shaikh, S, and Gunn, I. The nurse cystoscopist. Extending the role. British Journal of Perioperative Nursing 2005; 15(8): 342-345.

Reason: outcomes not relevant to PICO

Kent, DL et al. Evaluation of nonlinear optimization for scheduling of follow-up cystoscopies to detect recurrent bladder cancer. The Bladder Cancer follow-up Group. Medical Decision Making 1991; 11(4): 240-248.

Reason: outcomes not relevant to PICO

Nam, RK et al. Comparison of molecular and conventional strategies for followup of superficial bladder cancer using decision analysis. Journal of Urology 2000; 163(3): 752-757.

Reason: not relevant to PICO – health economics

Schmidbauer, J and Lindenau, G. Follow-up of nonmuscle invasive transitional cell carcinoma of the bladder: how and how often?. [Review] [32 refs]. Current Opinion in Urology 2008; 18(5): 504-507.

Reason: expert review

Schrag, D et al. Adherence to surveillance among patients with superficial bladder cancer. Journal of the National Cancer Institute 2003; 95(8): 588-597.

Reason: outcomes not relevant to PICO

Mazzonetto, M. Postcystectomy follow-up in bladder neoplasm and continent urinary diversion. The role of CT. Italian Current Radiology 1991; 10(3-4): 129-133.

Reason: foreign language

Abel, PD. Follow-up of patients with "superficial" transitional cell carcinoma of the bladder: the case for a change in policy. [Review] [41 refs]. British Journal of Urology 1993; 72(2): 135-142.

Reason: expert review

Hall, RR et al. Proposal for changes in cystoscopic follow up of patients with bladder cancer and adjuvant intravesical chemotherapy. BMJ 1994; 308(6923): 257-260.

Reason: expert review

Dubernard, JM et al. Correlation between cytology and cystoscopy in the follow-up of patients with bladder tumours. European Urology 1982; 8(1): 5-8.

Reason: outcomes not relevant to PICO

Gakis, G, Kruck, S, and Stenzl, A. Can the burden of follow-up in low-grade noninvasive bladder cancer be reduced by photodynamic diagnosis, perioperative instillations, imaging, and urine markers? Current Opinion in Urology 2010; 20(5): 388-392.

Reason: expert review

Mathers, MJ et al. Is there evidence for a multidisciplinary follow-up after urological cancer? An evaluation of subsequent cancers. World Journal of Urology 2008; 26(3): 251-256.

Reason: not relevant to PICO

Parmar, MK et al. Prognostic factors for recurrence and followup policies in the treatment of superficial bladder cancer: report from the British Medical Research Council Subgroup on Superficial Bladder Cancer (Urological Cancer Working Party). The Journal of urology 1989; 142: 284-288.

Reason: not relevant to PICO – prognostic factors

Aa, MN et al. Sexual function of patients under surveillance for bladder cancer. BJU International 2009; 104: 35-40.

Reason: not relevant to PICO – questionnaire completed before starting surveillance program

Gulliford, MC, Petruckevitch, A, and Burney, PG. Can efficiency of follow-up for superficial bladder cancer be increased? Annals of the Royal College of Surgeons of England 1993; 75(1): 57-61.

Reason: outcomes not relevant to PICO

Rabbani, F et al. Upper-tract tumors after an initial diagnosis of bladder cancer: argument for long-term surveillance. Journal of Clinical Oncology 2001; 19(1): 94-100.

Reason: recurrence not reported separately for NMIBC and MIBC/metastatic disease.

Taylor, J. An evaluation of a nurse-led cystoscopy surveillance service. Professional Nurse 2003; 18(10): 580-583.

Reason: not relevant to PICO

Lee, CT et al. Early-stage bladder cancer surveillance does not improve survival if high-risk patients are permitted to progress to muscle invasion. Urology 2007; 69(6): 1068-1072.

Reason: not relevant to PICO – follow-up schedule not reported

Chang, SS et al. Routine postoperative intensive care monitoring is not necessary after radical cystectomy. Journal of Urology 2002; 167(3): 1321-1324.

Reason: not relevant to PICO

Tran, W et al. Longitudinal risk of upper tract recurrence following radical cystectomy for urothelial cancer and the potential implications for long-term surveillance. Journal of Urology 2008; 179(1): 96-100.

Reason: method of UUT tumour detection not reported

Drake, R. Bladder cancer: Routine follow-up after radical cystectomy improves survival. Nature Reviews Urology 2010; 7(8): 419

Reason: comment on Giannarini 2010

Vrooman, OP and Witjes, JA. Follow-up of patients after curative bladder cancer treatment: guidelines vs. practice. Current Opinion in Urology 2010; 20(5): 437-442.

Reason: expert review

Wagner, KR et al. Prospective intermediate follow-up of carcinoma in situ involving the distal ureter at cystectomy: is there a role for ureteroscopy? Journal of Endourology 2008; 22(6): 1241-1246.

Reason: intervention not relevant to PICO

Hellenthal, NJ et al. The role of surveillance in the treatment of patients with muscle-invasive bladder cancer after chemotherapy. BJU International 2010; 105(4): 485-488.

Reason: not relevant to PICO

Gogus, C et al. 3-Dimensional computerized tomography in follow-up of patients with urinary diversion. International Urology & Nephrology 2005; 37(4): 739-742.

Reason: intervention not relevant to PICO, comparing 3D-CT with CT (no pathological findings)

Faithfull, S et al. Evaluation of nurse-led follow up for patients undergoing pelvic radiotherapy. British Journal of Cancer 2001; 85: 1853-1864.

Reason: Not relevant to PICO (nurse-led care versus control)

Soukup, V et al. Follow-up after surgical treatment of bladder cancer: a critical analysis of the literature. European Urology 2012; 62(2): 290-302.

Reason: Expert review

Boorjian, SA et al. Detection of asymptomatic recurrence during routine oncological followup after radical cystectomy is associated with improved patient survival. Journal of Urology 2011; 186(5): 1796-1802.

Reason: Relevant to another topic

Kuroda, M et al. Stage specific follow-up strategy after cystectomy for carcinoma of the bladder. International Journal of Urology 2002; 9(3): 129-133.

Reason: Relevant to another topic

Slaton, JW et al. A stage specific approach to tumor surveillance after radical cystectomy for transitional cell carcinoma of the bladder. Journal of Urology 1999; 162(3 Pt 1): 710-714.

Reason: Relevant to another topic

Yafi, FA et al. Surveillance guidelines based on recurrence patterns after radical cystectomy for bladder cancer: the Canadian Bladder Cancer Network experience. BJU International 2012; 110(9): 1317-1323.

Reason: Relevant to another topic

Segal, AJ et al. Follow-up imaging of bladder carcinoma. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000; 215 Suppl: 765-772.

Reason: Expert review

Volkmer, BG et al. Oncological followup after radical cystectomy for bladder cancer-is there any benefit? Journal of Urology 2009; 181(4): 1587-1593.

Reason: Relevant to another topic

Giannarini, G et al. Do patients benefit from routine follow-up to detect recurrences after radical cystectomy and ileal orthotopic bladder substitution? European Urology 2010; 58(4): 486-494.

Reason: Relevant to another topic

Kamat, AM et al. Prospective trial to identify optimal bladder cancer surveillance protocol: reducing costs while maximizing sensitivity. BJU International 2011; 108(7): 1119-1123.

Reason: Outcomes not relevant to PICO (sensitivity and Health economics)

Tahoun, NS, Abdel Maksoud, AM, and Mohamed, DB. Evaluation of the Value of Combined Urine Cytology and Cystoscopy for Follow-up of Superficial Transitional Cell Carcinoma of the Urinary Bladder. Journal of Egyptian National Cancer Institute 2010; 22(2): 105-111.

Reason: Outcomes not relevant to PICO (sensitivity)

Perlis, N et al. Upper urinary tract and urethral recurrences following radical cystectomy: review of risk factors and outcomes between centres with different follow-up protocols. World Journal of Urology 2013; 31(1): 161-167.

Reason: Relevant to another topic

Shinagare, AB, Sadow, CA, and Silverman, SG. Surveillance of patients with bladder cancer following cystectomy: yield of CT urography. Abdominal Imaging 2013; 38(6): 1415-1421

Reason: Relevant to another topic

Evidence tables

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Olsen 1995

Denmark</td>
<td>Randomised trial

1988-1993</td>
<td>102 (97 evaluable) all Ta G1-2 and free of recurrence at 3-mo cystoscopy after complete TUR</td>
<td>
<table>
<tr><th></th><th>Regimen 1</th><th>Regimen 2</th></tr>
<tr><td>N patients</td><td>45</td><td>52</td></tr>
<tr><td>Age</td><td>74.1</td><td>69.6</td></tr>
<tr><td>Male</td><td>35 (78%)</td><td>44 (85%)</td></tr>
<tr><td>Female</td><td>10 (22%)</td><td>8 (15%)</td></tr>
<tr><td>Median RFS (months)</td><td>28.9</td><td>26.9</td></tr>
<tr><td>Newly diagnosed</td><td>21 (47%)</td><td>24 (46%)</td></tr>
<tr><td>Recurrent</td><td>24 (53%)</td><td>28 (54%)</td></tr>
</table>
</td>
<td>Regimen 1: Follow-up every 3 mo for the 1st 2 years and every 6mo in the 3rd year. Once a year thereafter
Median f/up time: 30.6 months
Median no. of f/up visits: 8 (6-11)</td>
<td>Regimen 2: Follow-up every 6 mo for the 1st year and once a year thereafter
Median f/up time: 26.6 months
Median no. of f/up visits: 5 (4-7)</td>
<td>Median 30.6 mo regimen 1 and 26.6 mo regimen 2.</td>
<td>Transabdominal US performed at most follow-up visits. Unsuitable patients followed up by cystoscopy alone. Cystoscopy performed in all patients once a year.
Progression = Grade 3 or higher and/or tumour stage T1 or higher. Total number of follow-up visits reduced by 37.5% in regimen 2.
<table>
<tr><th></th><th>Regimen 1</th><th>Regimen 2</th><th>p-value</th></tr>
<tr><td>Median RFS (mo)</td><td>28.9</td><td>26.9</td><td>0.75</td></tr>
<tr><td>Recurrence</td><td>28 (62.2%)</td><td>26 (50%)</td><td>0.32</td></tr>
<tr><td>Progressed</td><td>3 (6.7%) (2 T1G3, 1 TaG3)</td><td>1 (1.9%) (TaG3)</td><td>0.49</td></tr>
<tr><td>Tumour mortality</td><td>0</td><td>0</td><td>-</td></tr>
<tr><td>Overall mortality</td><td>5 (11.1%)</td><td>2 (3.8%)</td><td>0.33</td></tr>
</table>
</td>
<td>NR</td>
<td>Adequate randomisation and sequence generation. Blinding not reported.</td>
</tr>
<tr>
<td>Yossepowitch 2007
USA</td>
<td>Qualitative study

Jan – Apr 2006</td>
<td>200 NMIBC undergoing flexi cystoscopy as follow-up</td>
<td>
<table>
<tr><th></th><th>N (%)</th></tr>
<tr><td>N patients</td><td>200</td></tr>
<tr><td>Median Age</td><td>68</td></tr>
<tr><td>Age range</td><td>21-91</td></tr>
<tr><td>Male</td><td>119 (60%)</td></tr>
<tr><td>Female</td><td>81 (40%)</td></tr>
<tr><td>PUNLMP</td><td>6 (3)</td></tr>
<tr><td>Tis</td><td>19 (9)</td></tr>
<tr><td>Ta</td><td>108 (54)</td></tr>
<tr><td>T1</td><td>50 (25)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Low grade</td><td>88 (44)</td></tr>
<tr><td>High grade</td><td>112 (56)</td></tr>
</table>
</td>
<td>Patient interviewed to assess anxiety and pain related to follow-up cystoscopy.</td>
<td>NA</td>
<td>NA</td>
<td>Pain reported on a 10-point self-assessment scale. 74% reported none or minimal pain (0-2). Higher pain scores reported by 17 patients undergoing fulguration compared to those undergoing cystoscopy alone (p<0.0005). 9 patients with fulguration (53%) indicated none or minimal pain. Only 7 patients (3.5%) were prepared to use a biomarker with an accuracy of 80% or less due to anxiety associated with the possibility of missing a cancer.</td>
<td>NA</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td><table>
<tr><td></td><td></td></tr>
<tr><td colspan="2">Surveillance cystoscopy schedule</td></tr>
<tr><td>Every 3mo</td><td>57 (28)</td></tr>
<tr><td>Every 4mo</td><td>25 (13)</td></tr>
<tr><td>Every 6mo</td><td>96 (48)</td></tr>
<tr><td>Every 12mo</td><td>22 (11)</td></tr>
</table></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>van der Aa (2008) Netherlands</td><td>Cross-sectional questionnaire</td><td>201 NMIBC from trial comparing cystoscopic surveillance with microsatellite analysis</td><td><table>
<tr><td></td><td>CUS</td><td>MA</td></tr>
<tr><td>Response</td><td>108 (99)</td><td>93 (85)</td></tr>
<tr><td>Male</td><td>79 (73)</td><td>72 (77)</td></tr>
<tr><td colspan="3">Previous cystoscopies</td></tr>
<tr><td>1</td><td>16 (15)</td><td>20 (22)</td></tr>
<tr><td>2-5</td><td>45 (41)</td><td>32 (34)</td></tr>
<tr><td>>5</td><td>47 (44)</td><td>41 (44)</td></tr>
<tr><td colspan="3">Previous TURs</td></tr>
<tr><td>1</td><td>72 (67)</td><td>47 (50)</td></tr>
<tr><td>2-5</td><td>25 (23)</td><td>35 (38)</td></tr>
<tr><td>>5</td><td>11 (10)</td><td>11 (12)</td></tr>
<tr><td>Mean age</td><td>68.3 yrs</td><td>68.2 yrs</td></tr>
</table></td><td>3-monthly cystoscopy for 24 mo Patients completed questionnaires 1 week after cystoscopy or 1 week after collection of a urine sample for microsatellite analysis (MA).</td><td>3-monthly MA for 24mo. Cystoscopy also at 3, 12 and 24 mo.</td><td>NA</td><td><table>
<tr><th>Rating</th><th>N (%) No</th><th>N (%) Quite</th><th>N (%) Very</th></tr>
<tr><td>Discomfort</td><td></td><td></td><td></td></tr>
<tr><td>Introduction</td><td>424 (61)</td><td>229 (33)</td><td>44 (6)</td></tr>
<tr><td>Undergoing</td><td>472 (68)</td><td>193 (28)</td><td>30 (4)</td></tr>
<tr><td>After cystoscopy</td><td>517 (74)</td><td>151 (22)</td><td>33 (5)</td></tr>
<tr><td>Pain</td><td></td><td></td><td></td></tr>
<tr><td>Introduction</td><td>455 (66)</td><td>215 (31)</td><td>25 (4)</td></tr>
<tr><td>Undergoing</td><td>544 (78)</td><td>135 (19)</td><td>19 (3)</td></tr>
<tr><td>After cystoscopy</td><td>535 (76)</td><td>152 (22)</td><td>15 (2)</td></tr>
<tr><td>Painful void</td><td>500 (70)</td><td>206 (29)</td><td>13 (2)</td></tr>
<tr><td>Urge + freq</td><td>472 (66)</td><td>194 (27)</td><td>49 (7)</td></tr>
<tr><td>Fever >38°C</td><td>709 (99)</td><td>9 (1)</td><td>0</td></tr>
<tr><td></td><td>No</td><td>Yes, some</td><td>Yes, a lot</td></tr>
<tr><td>Haematuria</td><td>664 (93)</td><td>47 (7)</td><td>7 (1)</td></tr>
<tr><td>Urine test Discomfort</td><td>No</td><td>Quite</td><td>Very</td></tr>
<tr><td>Collection</td><td>158 (98)</td><td>2 (1.3)</td><td>1 (0.6)</td></tr>
<tr><td>Delivery</td><td>168 (98)</td><td>4 (2.4)</td><td>0</td></tr>
<tr><td>Awaiting result</td><td>130 (81)</td><td>24 (14.9)</td><td>7 (4.3)</td></tr>
<tr><td></td><td>No</td><td>Yes< 7</td><td>Yes>7</td></tr>
</table></td><td>NA</td><td></td></tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							Painful void 155 (88) **days** 19 (11) **days** 2 (1.1) Urge + freq 132 (75) 30 (17) 15 (8.5) Fever >38˚C 175 (98) 3 (1.7) 0 **No** **Yes, some** **Yes, a lot** Haematuria 166 (93) 10 (6) 2 (1)		
Vriesema 2000 Netherlands	Cross-sectional questionnaire/ interview study March-Nov 1999	102 NMIBC	Patients with known NMIBC for at least one year undergoing flexible cystoscopy follow-up Mean age 67.5 yrs (range 38-83). 10% undergone 5 or fewer cystoscopies, 31% 5-10, 59% 10+. 29% never had recurrence, 19% had 1 recurrence, 52% had multiple recurrences.	Questionnaire about experience with flexible cystoscopy, preferences for cystoscopy or urine test, complications with procedure	NA	NA	Not bothersome 29/85 (34%); somewhat bothersome 45/85 (53%); very bothersome 11/85 (13%). No differences in age or gender. Only 9 patients (11%) were prepared to use a urine test with an accuracy of 85% or less due to anxiety associated with the possibility of missing a cancer. 68% required accuracy of 99-100%	NA	
Stamatiou 2011 Greece	Prospective diagnostic study Apr-Nov 2007 & Sep 2008 – Feb 2009	33 recurrent NMIBC. Excluded previous CIS	Median age 76 (range 56 to 81) 29/33 (88%) male. Low risk of recurrence and progression (n=16), high risk (n=7), intermediate risk (n=10).	Transabdominal US and urinary tract abdominal US. Colour or spectral Doppler imaging performed. Diagnostic criteria – presence of irregular soft tissue of low to intermediate echo texture projecting into the bladder lumen from a fixed mural site	Cystoscopy (CS) performed immediately after US. Rigid CS 16 to 25Fr, without knowledge of US.	NA	Patients with US and/or CS findings suggestive of cancer were further evaluated with TUR. Confirmation of bladder cancer from histopathologcal examination of biopsy 14/33 (42.4%) bladder cancer recurrence. 19% (n=3) low risk; 86% (n=6) high risk; 50% (n=5) intermediate risk. 11 patients had abnormal bladder US (78.6%). 2/3 cancers missed by US and found by CS were smaller than 3mm. The other was located in the inner part of the diverticulum. Sensitivity of US=78.5%, specificity=100%, PPV=100%, NPV = 86.3%. 17 (51.5%) patients reported excessive discomfort-low tolerability for CS, 9 (27.2%) reported moderate discomfort, 7 (21.2%) reported no discomfort	No conflicts of interest reported	No details about primary cancer, prior f/up, number of recurrences, or prior treatment

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Vallancien 1986
France</td>
<td>Appears prospective</td>
<td>100 who had undergone 1 or more TURBT (stage Pa or P1).</td>
<td>Excluded CIS, high grade tumours or MIBC.</td>
<td>Suprapubic US followed by cytology and CS performed 3 to 9 mo after last resection. Bladder examined in the transverse, sagittal and oblique planes.</td>
<td>US versus CS</td>
<td>NA</td>
<td>Correlation between US and CS in 81/100 (81%) patients.
<table>
<tr><th>N patients</th><th>US</th><th>CS</th><th>Cytology</th></tr>
<tr><td>31</td><td>Pos</td><td>pos</td><td>Pos</td></tr>
<tr><td>38</td><td>neg</td><td>neg</td><td>Neg</td></tr>
<tr><td>12</td><td>pos</td><td>pos</td><td>Neg</td></tr>
<tr><td>4</td><td>pos</td><td>neg</td><td>Neg</td></tr>
<tr><td>15</td><td>neg</td><td>pos</td><td>9n,6p</td></tr>
</table>
4 False +ve with US, 15 false –ve, overall sensitivity 90%, specificity 74%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Mariappan 2005
UK</td>
<td>Review of prospective records 1978-1985</td>
<td>115 pTaG1. Excluded upper tract involvement</td>
<td>
<table>
<tr><th></th><th>N (%)</th></tr>
<tr><td>Mean Age</td><td>64.6</td></tr>
<tr><td>Age range</td><td>27-84</td></tr>
<tr><td>Male</td><td>72 (63)</td></tr>
<tr><td>Female</td><td>43 (37)</td></tr>
<tr><td>Single</td><td>86 (75)</td></tr>
<tr><td>3 or more</td><td>18 (16)</td></tr>
<tr><td>≤10mm</td><td>62 (54)</td></tr>
<tr><td>10-30mm</td><td>32 (28)</td></tr>
<tr><td>≥30mm</td><td>21 (18)</td></tr>
</table>
20 patients received intravesical thiotepa or MMC as part of MRC trial. Recurrences treated with TUR or biopsy with diathermy.</td>
<td>Rigid cystoscopy – 1st check at 3mo, 6/9mo then annually. All suspicious lesions and tumour were biopsied before definitive treatment</td>
<td>NA</td>
<td>Mean 10.9 years for 32 patients who died. 83 patients had mean f/up of 23.1 yrs (range 19-27)</td>
<td>Recurrence: Significant decrease in recurrence after 5-yrs of f/up (29.1% versus 14.1%, p=0.009). The 5 and 10 year RFS = 50.9% and 42.4%. 58 (50.4%) had at least 1 recurrence throughout f/up. Of these, 49 (85.9%) recurred within 1 year. Of 66 patients who reached year 1 without recurrence, 9 had a recurrence later (14% risk). Only one patient had first recurrence after year 5 (0.87%) – the area was too small to justify diathermy to the base. Of the 66 who were tumour free at 3 mo and 1 yr, 8 had recurrence by year 5 (all TaG1, less than 5mm). Recurrence at 3 mo associated with recurrence at 1yr (55% vs 17.8%). Recurrence rate of those with tumour at 3mo remained persistently higher. 98.3% of those who did not have recurrence in 5 years remained tumour-free for 20 yrs.
Progression: 14 (12.2%) progression on f/up, 7 (50%) within 1 yr and 5 (37.5%) in the 3mo first cystoscopy. All patients who progressed had multiple primaries and multiple recurrences. 8 TaG2, 4 T1, none progressed to MIBC. No patient who was recurrence free in year 1 went on to have progression. No deaths from bladder cancer.</td>
<td>NA</td>
<td>Results for TaG2 reported by Mariappan in abstract only with no significant difference between trends for TaG1 and TaG2</td>
</tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Holmang 2002 Sweden	Retrospective review 1987-1988	355 Ta-T1 with at least 5yrs follow-up (out of 680 consecutive patients)	Excluded primary CIS. Patients treated with TUR only until the 2nd follow-up cystoscopy after the initial diagnosis. Excluded patients with 1st cystoscopy later than 5 mo after diagnosis	Mean time to 1st cystoscopy after TUR was 112 days (range 40-150)	NA	At least 5 years	**Recurrence:** Patients with PUNLMP and negative 1st cystoscopy - 68% remained tumour free during follow-up vs 29% of those with recurrence at 1st cystoscopy. G1 and neg cystoscopy vs G1 and pos 1st cystoscopy - 36% vs 8% tumour free, G2 51% vs 15% and G3 36% vs 6%. Multivariate analysis showed that first cystoscopy finding and grade were independent predictors of recurrence. **Progression:** First cystoscopy findings and grade were also independent predictors of progression.	NA	Frequency/ duration of follow-up not reported.
LeBlanc 1999 Canada	Review of prospective records 1974-1994	152 TaG1	Mean age 61 (range 25 to 87). 109 (72%) male, 43 (28%) female. All underwent TURBT at initial diagnosis. 20 patients received intravesical therapy – BCG, MMC or thiotepa.	Cytology and cystoscopy every 3mo and every 6 mo if tumour free for 2 years. Yearly cystoscopy if 4yrs elapsed without recurrence	NA	Mean 76 mo (range 6 to 241)	**Recurrence:** 83/152 (55%) had 1 or more recurrences. Median interval between diagnosis and first recurrence was 14 months (range 3 to 161). Of 49 patients with first recurrence within 24 mo, 38 (78%) had multiple recurrences, and 11 (22%) had single recurrence. Of the 34 patients tumour-free for 24 months or more, 16 (47%) had single recurrence and 18 (53%) had multiple recurrence. Patients who remained tumour free at 1 year had a 43% risk of recurrence. After remaining tumour free for 2-10 years recurrence rate was 30%. **Progression:** 31/152 (20%) progressed. 2 progressed to G2 tumour, 2 to grade 3, 3 to CIS, 5 to MIBC. Risk of progression in grade remained fairly constant over 10 years at 20%. Lower rate of progression in stage (6%).	NA	
Zieger 2000 Denmark	Retrospective review	217 Ta cancer followed up for at least 1yr	154 male, mean age 66 (range 34-84). 63 women, mean age 67 (range 20-87). 33 G0-1, 179 G2, 5 G3. Mostly single and <3cm tumour. Treatment was TURBT. 10 received intravesical thiotepa, 2 received	Cystoscopy every 4th month until recurrence free for 5 years.	NA	Mean 84 months, max 238 mo	**Recurrence:** 61% overall recurrence rate. After recurrence free period (RFP) of 1 year, the cumulative probability was 46%, after RFP 2 years it was 34%. 85 (39%) had no recurrence, 43 (20%) had less than one recurrence per year. 41% recurred frequently.	NA	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			radiotherapy, 4 received BCG (after 1987)				**Progression:** 42 (19%) tumours had invasive potential: 19 T1, 23 (11%) showed MIBC or distant mets. No G1 tumours progressed but 6 converted to G2. 10 TaG2 converted to TaG3 or CIS. Median time to progression = 55 (3-209) months. **Survival:** 23 died from bladder cancer related causes, inc 3 with no muscle invasion. **UUT recurrence:** 15 (7%) had UUT after a mean of 52 months – 9 of these were invasive (T1+)		
Oge 2000 Turkey	Retrospective review of prospectively kept records 1984-1997	120 pTa G1-2 with at least 9 mo f/up. Excluded tumours >4cm	Mean age at diagnosis=56.5yrs (range 21-84). 88/120 solitary tumours, 32 multiple. 86 G1, 34 G2. All tumours resected completely and random biopsies obtained during 1st evaluation.	3-monthly f/up under general anaesthesia for 2 years, then every 6mo for 2 yrs then annually if no tumour detected	NA	Mean 36mo (9-156)	**Recurrence:** 3-mo recurrence rate = 8/120 (6.5%); 6-mo 8/119 (6.7%); 9-mo 4/112 (3.6%); 12-mo 8/99 (8%). For tumours with no recurrence at 3-mo, the recurrence rate at 6 mo = 5/112 (4.3%); 9-mo 3/110 (2.7%) G1 tumours: recurrence rate at 3,6,9, 12 mo = 6% (5/84); 6% (5/83); 2.5% (2/80); 7% (5/71) G2 tumours: 8% (3/36); 8% (3/36); 6% (2/32); 10.5% (3/28). No significant difference between recurrence rate in G1 and G2. Recurrence rate at any time of the 1st year had no prognostic value for the outcome of the following cystoscopy. In patients with follow-up of >2yrs, overall recurrence rate was 9% (7/78) in the 2nd year – of these only 1 had a small and solitary tumour at diagnosis. **Progression:** Only one case of progression at 6-month cystoscopy.	NA	
Thompson 1993 USA	Retrospective cohort study 1989-1991	20 Ta-T1 with at least 5yrs surveillance without tumour (out of 124 consecutive patients)	Mean age 65 (range 52-75). Average interval after resection of initial tumour = 8.1 years (range 5.3 to 12.4) Ta (n=7), Ta (n=13), G1 (n=16), G2 (n=4)	Cystoscopy and cytology every 3mo for 1yr, then every 6mo for 1 yr, and annually thereafter. Patients with	NA	Average interval after initial TUR = 8.1yrs (range 5.3-12.4)	**Progression:** 7/20 (stage Ta in 4, T1 in 3) patients had MIBC 6.8 years (range 5.3 to 9.1) after initial tumour resection. All 7 had G1 at initial resection. All patients underwent radical cystectomy and ileal conduit diversion, and all organ-confined disease. All 7 patients were alive with no evidence of disease at 18 months to 5 years after cystectomy.	NA	No details of treatment received.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
				MIBC were evaluated with CT of chest, abdomen, pelvis and bone scan and liver function test.					
Holmang 2012 Sweden	Retrospective cohort study 1986-2003	542 BCG treated NMIBC. 39% maintenance treatment.	<table><tr><th></th><th>All patients</th><th>Tumour-free >5yr</th></tr><tr><td>N (%)</td><td>542</td><td>204 (37)</td></tr><tr><td>Males (%)</td><td>76.9</td><td>80.9</td></tr><tr><td>Median age</td><td>72</td><td>68</td></tr><tr><td>Primary</td><td>141</td><td>59 (42)</td></tr><tr><td>Recurrent</td><td>401</td><td>145 (36)</td></tr><tr><td>Solitary</td><td>75</td><td>35 (48)</td></tr><tr><td>Multiple</td><td>355</td><td>117 (35)</td></tr><tr><td>Grade 1</td><td>108</td><td>41 (38)</td></tr><tr><td>Grade 2</td><td>175</td><td>69 (39)</td></tr><tr><td>Grade 3</td><td>127</td><td>42 (33)</td></tr><tr><td>CIS only</td><td>132</td><td>52 (38)</td></tr><tr><td>Ta w/out CIS</td><td>237</td><td>89 (40)</td></tr><tr><td>T1 w/out CIS</td><td>83</td><td>33 (37)</td></tr><tr><td>TA/T1 + CIS</td><td>90</td><td>30 (34)</td></tr><tr><td>Previous chemo</td><td>22</td><td>7 (31)</td></tr><tr><td>Previous UTT</td><td>40</td><td>9 (23)</td></tr><tr><td>Previous RT</td><td>17</td><td>4 (24)</td></tr><tr><td>Intermediate risk recurrence</td><td>291</td><td>111 (38)</td></tr><tr><td>High risk recurrence</td><td>115</td><td>39 (34)</td></tr><tr><td>Intermediate risk progression</td><td>218</td><td>83 (38)</td></tr><tr><td>High risk progression</td><td>188</td><td>67 (36)</td></tr></table>	Cystoscopy and cytology every 3-6mo for 2-3 years, followed by yearly examinations. F/up terminated after 10-20 tumour-free years. UT imaging only performed in cases with macroscopic haematuria or unexplained malignant cytology.	NA	At least 5 years	**Recurrence:** Recurrences per year = 0.36. 338 were not tumour-free for 5yr. Of them 81 (24%) progressed in stage. UT tumour in 30/338 (8.9%). 204 patients tumour free for a continuous period of ≥60 months since 1st BCG instillation. 74/204 (36.3%) had a recurrence during the first 5 yr after BCG treatment, followed by a tumour-free period of ≥5yr. 22/204 (10.8%) had recurrence after being tumour-free for ≥5years. For those with ≥5 tumour-free yrs - At 10 years after BCG 82.3% TaG1-TaG2 and 91.3% TaG3/CIS/T1 remained tumour-free. At 15 years 65.4% and 86% were tumour-free. Primary versus recurrent tumour before BCG was the only significant variable for late recurrence. A multivariate analysis was not performed. **Survival:** 57 (10.5%) died during first 5yr from urothelial cancer and 96 (17.7%) from intercurrent disease. Between years 6-25, 32 (5.9%) died from urothelial cancer and 150 (27.7%) died from intercurrent disease. In June 2011 207/542 (38.2%) were still alive.	NA	
Miyake 2006 Japan	Retrospective cohort study	413 NMIBC	<table><tr><th></th><th>UUT -ve</th><th>UUT +ve</th></tr><tr><td>N patients</td><td>393</td><td>20</td></tr></table>	Cystoscopy and cytology every	NA	Median 102	20/413 (4.8%) upper tract tumours were detected. The median (range) time from initial	NA	

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td></td>
<td>1986-2003</td>
<td></td>
<td>
<table>
<tr><td>Age <70</td><td>253</td><td>12</td></tr>
<tr><td>≥70</td><td>140</td><td>8</td></tr>
<tr><td>Male</td><td>312</td><td>14</td></tr>
<tr><td>Female</td><td>81</td><td>6</td></tr>
<tr><td>Papillary</td><td>363</td><td>18</td></tr>
<tr><td>Other</td><td>30</td><td>2</td></tr>
<tr><td>≤3cm tumour</td><td>304</td><td>15</td></tr>
<tr><td>≥3cm</td><td>89</td><td>5</td></tr>
<tr><td>Solitary</td><td>261</td><td>7</td></tr>
<tr><td>Multiple</td><td>132</td><td>13</td></tr>
<tr><td>G1</td><td>99</td><td>5</td></tr>
<tr><td>G2</td><td>265</td><td>14</td></tr>
<tr><td>G3</td><td>29</td><td>1</td></tr>
<tr><td>Ta</td><td>261</td><td>13</td></tr>
<tr><td>T1</td><td>132</td><td>7</td></tr>
<tr><td colspan="3">Concomitant CIS</td></tr>
<tr><td>Yes</td><td>38</td><td>4</td></tr>
<tr><td>No</td><td>355</td><td>16</td></tr>
<tr><td colspan="3">Adjuvant chemo</td></tr>
<tr><td>Yes</td><td>48</td><td>4</td></tr>
<tr><td>No</td><td>345</td><td>16</td></tr>
<tr><td colspan="3">BCG therapy</td></tr>
<tr><td>Yes</td><td>41</td><td>4</td></tr>
<tr><td>No</td><td>352</td><td>16</td></tr>
</table>
</td>
<td>3mo for 2yrs after TUR, then every 6mo at 3-5yrs and then annually thereafter. IVU every 6mo until 3yrs after TUR and then annually until 5 yrs. At 5yrs the examinations were at the patients request</td>
<td></td>
<td>months</td>
<td>TUR to diagnosis of subsequent UUTCs was 33 (6-165) months.
No differences between patients in age/gender/growth pattern/grade/stage/tumour size/CIS/chemo or BCG therapy. Patients with UUT recurrence had a higher incidence of multiple tumour at initial TUR than those with no recurrence. No independent predictors for UUT recurrence.
Only 2 patients were diagnosed as having UUTC by routine IVU. The remaining 18 presented with symptoms which were an incentive to examin the UUT by extra IVU (macrohaematuria 10, intravesical recurrence 5, +ve urine cytology 5, abdominal pain 3, high fever 2)
IVU after detecting some symptoms failed to show findings suspicious of recurrent UUTCs in 10 of 18 patients and these 10 were diagnosed by other methods inc retrograde pyelography, CT and/or ureterorenoscopy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holmang 1998
Sweden</td>
<td>Retrospective cohort study 1987-1988</td>
<td>680 with bladder cancer (497 NMIBC)</td>
<td>Not reported</td>
<td>All patients had excretory urography (IVP) before diagnostic TUR and every 3rd year during f/up. Annual IVP recommended for patients with multiple or recurrent tumours and those treated</td>
<td>NA</td>
<td>At least 5years</td>
<td>
<table>
<tr><th>Grade/stage</th><th>N patients</th><th>N UTT/ person yrs follow-up</th></tr>
<tr><td>TaG1</td><td>255</td><td>4/1265</td></tr>
<tr><td>TaG2</td><td>95</td><td>5/471</td></tr>
<tr><td>Ta/G3/CIS</td><td>25</td><td>1/108</td></tr>
<tr><td>T1 G1-G2</td><td>53</td><td>2/216</td></tr>
<tr><td>T1G3</td><td>69</td><td>1/283</td></tr>
</table>
16 patients in total diagnosed with renal pelvis or ureteral carcinoma. Median interval = 30 months (range 6-74). 7 presented with gross haematuria, and 3 with abdominal pain and fever.
IVP between 0-10 months before UUT was</td>
<td>NA</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>with RT or RC</td><td></td><td></td><td>diagnosed did not detect tumour in 8/16 patients.
Survival – 13 patients died at time of most recent follow-up, median 13 mo (range 2-59) after diagnosis of UUT. 11 (69%) died of cancer or complications following RT.</td><td></td><td></td></tr>
<tr><td>Hession 1999
UK</td><td>Retrospective cohort study</td><td>174 with bladder cancer (140 NMIBC)</td><td>132 male, mean age 59 (range 20-84).
Average number of IVUs per patient = 3.7</td><td>IVU routinely performed. No further details</td><td>NA</td><td>Median 8.3 yrs (range 1-30)</td><td>102 (58.6%) had normal IVU at presentation. Commonest abnormality on IVU was a bladder filling defect (61, 35.1%).

No synchronous UTT were found. Of the 164 patients evaluated cystoscopically at 12mo, 83 (50.6%) had recurrent TCC of the bladder. 156 patients (95%) had normal IVU at this time.

6 (5/6 NMIBC) patients had proven UUT, mean 78 mo (range 12-132) post presentation . 5/6 had solitary tumour at presentation. All of those who subsequently developed UTT had recurrent bladder tumour within 24 months. 4/6 UUT occurred at 72 months or later.</td><td>NA</td><td>No details of treatment received.</td></tr>
<tr><td>Canales 2006
USA</td><td>Retrospective cohort study</td><td>375 with primary Ta bladder TCC. T1 and CIS excluded</td><td>Initial evaluation and treatment consisted of UT imaging and complete TUR. No intravesical therapy.

<table><tr><th></th><th>Number</th><th>% affected</th></tr><tr><td colspan="3">Initial No. bladder tumours</td></tr><tr><td>1</td><td>183</td><td>49</td></tr><tr><td>2</td><td>107</td><td>29</td></tr><tr><td>3</td><td>55</td><td>15</td></tr><tr><td>4+</td><td>30</td><td>7</td></tr><tr><td colspan="3">Highest grade of initial bladder</td></tr><tr><td>1</td><td>85</td><td>23</td></tr><tr><td>2</td><td>192</td><td>51</td></tr><tr><td>3</td><td>98</td><td>26</td></tr><tr><td colspan="3">No. recurrences</td></tr><tr><td>0</td><td>183</td><td>48</td></tr></table></td><td>Cystoscopy and cytology every 3mo for 2yr, every 6mo for 2yr, then yearly until next recurrence. UT imaging by IVP, retrograde pyelography or CT urogram once or twice in 1st 5years (typically every 2-3 yrs) after TUR.</td><td>NA</td><td>Median 58 mo (range 14-176)</td><td>50% had no recurrent bladder tumour. 25% had 1 tumour, 15% had 2 tumours and 10% had 3 or more tumours.

72% underwent 1 (45%) or 2 (27%) screening studies of the UUT in the 1st 5 years. 28% had no UT imaging. Most imaging by IVP (86%), though some had ultrasound followed by retrograde pyelogram (10%) or CT (4%).

13 (3.4%) developed UUT occurrence after a mean 22 months. Time to recurrence and number of bladder tumours were statistically significant predictors of UUT disease.

7/13 with UUT tumour – 7 identified by imaging</td><td>NA</td><td></td></tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			1 102 26 2 57 17 3+ 33 9				while the remaining 6 had gross haematuria, microscopic haematuria, or +ve cytology. 3/6 had been screened once with imaging before presenting with UUT later on. 5/7 identified by imaging were alive and no evidence of disease (NED), 1 died with NED, 1 died of disease. Of 6 UT tumours identified by other methods, 3 died of disease, 3 were alive with disease.		
Sternberg 2013 USA	Retrospective review 2000-2006	935 with NMIBC without concomitant UUTT	N (%) Median age 66 years Male 702 (75) Female 233 (25) Primary Ta 481 (51) Primary T1 454 (49) CIS 355 (38) TURBT+IVT 682 (73%) Cystectomy 226 924)	Reports of imaging were included if performed for UT surveillance, not for signs or symptoms of UTT. Imaging performed at discretion of physician. Over 90% were CT imaging.	n/a	Median follow-up in patients without diagnosis 5.5y	51/935 patients had a recurrence. 5-year UTT-free among TA patients was 98% and 93% among patients with T1 disease. UUT developed in 29 patients within 5 years of the first episode of NMIBC. UUT in 16 patients with TA (10 after symptoms, 4 on routine imaging) UUT in 33 patients with T1 (20 after symptoms, 9 on routine imaging) Overall 3074 routine CT studies were performed, of which UUT was diagnosed in 15 (0.49%).	NR	Not all imaging was CTU.

Health Economic Evidence: What are the optimal follow-up protocols for low/intermediate risk and high-risk non-muscle invasive bladder cancer?

Background

There is general agreement that patients with non-muscle invasive bladder cancer (NMIBC) require regular cystoscopic surveillance of their bladder to check for recurrence. However, there is no agreement upon the optimal frequency and length of cystoscopic follow-up and, as such, there is significant variation in clinical practice.

Tailoring follow-up strategies based on risk could allow for follow-up to be safely reduced in the lower risk groups whilst ensuring that the higher risk patients are still monitored closely. In addition, the use of alternative tests to cystoscopy, such as urinary biomarkers and cytology, could have a useful role in reducing the burden of cystocopies. However, the effectiveness and cost-effectiveness of such approaches has never been reliably demonstrated.

Aims

To estimate the cost-effectiveness of reduced follow-up and/or follow-up using newer tests and techniques in comparison to the test and protocols used in current practice in NMIBC patients.

Existing Economic Evidence

A systematic literature review did not identify any cost-utility analyses that sufficiently addressed the current decision problem. However, three papers were identified that utilised modelling techniques to compare follow-up strategies; De Bekker Grob et al. 2009, Van Kessel et al. 2013 and Zhang et al. 2013. microsatellite analysis

De Bekker Grob et al. 2009 constructed a semi-Markov model to investigate two strategies; a conventional strategy consisting of cystoscopy every 3 months and a test arm consisting of microsatellite analysis of voided urine samples every 3 months with a control cystoscopy at 3, 12 and 24 months. The authors found that the probability of being without recurrence after 2 years was similar in the two groups but the total costs were higher in the test arm. Further analysis suggested that the test arm would be as effective and cost the same as the conventional arm if the sensitivity increased to ≥61%, the specificity was set to 73% and the costs were decreased from €158 to <€70. The authors concluded that cystoscopy could be partly replaced if the microsatellite analysis urine test had a higher sensitivity and its costs were reduced.

A similar analysis was conducted by Van Kessel et al. 2013, in which three surveillance strategies were compared using a Markov model; standard surveillance defined as cystoscopy every three months, minimal surveillance defined as cystoscopy at 3, 12 and 24 months and modified surveillance consisting of FGFR3 mutation analysis of voided urine samples every 3 months and cystoscopy at 3, 12 and 24 months. The authors found that the probability of no recurrence after two years of surveillance was higher for the modified surveillance than the standard or minimal surveillance arms. The total cost of surveillance was found to be lower for minimal and modified surveillance than for standard surveillance. The authors concluded that surveillance in which

cystoscopy is partly replaced by FGFR3 mutation analysis of urine seems a safe, effective and cost-effective surveillance strategy.

The analysis conducted by Zhang et al. 2013 compared surveillance strategies for low risk NMIBC patients. The study was not a cost-effectiveness analysis and indeed did not even consider costs but it did estimate QALYs for each strategy. The authors developed a Markov model to compare surveillance strategies recommended in international guidelines and additional proposed strategies. The authors found that age and co-morbidities significantly affect the optimal surveillance strategy. The results suggested that younger patients should be screened more intensively than older patients and patients with co-morbidities should be screened less intensively.

De Novo Economic Model

Since the current economic literature did not adequately address the decision problem[6], a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel.

Patients were assumed to enter the model in a 'disease free' state following an initial transurethral resection of the bladder tumour (TURBT). At each 3-monthly model cycle the patient may experience a bladder cancer recurrence. If the recurrence is detected, the patient will undergo a further TURBT (or fulguration of the tumour) and return to a disease free state. However, if the recurrence is not detected, then the patient will be at risk of progression and will have to undergo further treatment once this progression is eventually detected (cystectomy and possibly neo-adjuvant chemotherapy). The patient may also die from bladder cancer related mortality after experiencing progression and may die from other cause mortality from any health state.

Estimated total costs and quality adjusted life years (QALYs) were collected over the modelled 10 year time horizon for each follow-up strategy. Future costs and benefits were discounted at a rate of 3.5% per year as recommended by NICE.

The risk of recurrence and progression in patients with NMIBC was estimated using risk equations based on an analysis of 2,596 patients from seven EORTC[7] trials (Sylvester et al. 2006). Patients are 'scored' based on a number of risk factors, such as number of tumours, tumour size, prior recurrence rate, T category, presence of CIS and grade. An individual's one year and five year risks of recurrence and progression can then be estimated based upon these scores.

For the purposes of the economic model, it was necessary to convert these five year and one year risks into 3-monthly risks. The higher risk of recurrence and progression in the first year was captured by calculating separate 3 monthly risks for the first year and subsequent years (based on the one year risk and five year EORTC risks). Furthermore, since the EORTC risk equations consider recurrence and progression *independently*, it was necessary to link the progression rates to the recurrence rate i.e. estimate the *probability of progression given recurrence* in each of the risk groups.

[6] It should be noted that, while none of the above studies met the requirements for inclusion in the systematic review, they were nonetheless informative in helping to develop our own de novo economic model.
[7] European Organisation for Research and Treatment of Cancer

The table below shows the three monthly risks of recurrence, progression and progression given recurrence applied for each of the risk groups in the base case analysis.

Table 97: Three Monthly Recurrence And Progression Risk Applied In The Model

Outcome	3 monthly rates		
	Recurrence	Progression given recurrence	Progression
First year			
Low risk	3.98%	1.26%	0.05%
Intermediate risk	6.63%	3.78%	0.25%
High risk – Lower	11.26%	11.31%	1.27%
High risk – Upper	20.97%	21.70%	4.55%
Subsequent years			
Low risk	1.84%*	2.18%*	0.04%*
Intermediate risk	3.03%	10.18%	0.31%
High risk – lower	4.72%	19.64%	0.93%
High risk – upper	7.29%	40.39%	2.94%

*In low risk patients, rates of recurrence and progression in years 6-10 are assumed to be zero

As the modelled time horizon of 10 years exceeds the predicted risk estimates from the EORTC trials (5 years), it was also necessary to make some assumptions about the risk profile of patients in years 5-10. In the base case, it was assumed that the subsequent year rate (i.e. years 2-5) would be maintained in years 6-10 except in the case of low-risk patients in whom it was assumed that risk would be zero after 5 years (reflecting clinical practice of discharging low-risk patients from follow-up after 5 years).

Bladder cancer related mortality rates were estimated using data from a systematic review by Van den Bosch et al. 2011. Using the data in the study, separate three mortality rates were estimated for patients that progressed to muscle invasive disease and those that remained non-muscle invasive following a cystectomy (3.6% and 0.5%, respectively). The lower rate in NMIBC patients reflects an assumption that patients would have to first progress to MIBC before dying of bladder cancer.

Death from other causes was captured using 2009-2011 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender with the model assuming that 50% of patients were female and that the average age was 60 years old. These annual probabilities were converted to three-monthly probabilities for use in the model.

Follow-up strategies

The variations in the frequency of follow-up that were considered in the model are summarised below.

Table 98: Variations In The Frequency Of Follow-Up That Are Considered In The Model

Risk group	Follow-up strategy		
	Current practice	**Slightly reduced frequency**	**Reduced frequency**
Low risk	Cystoscopy at 3 months, 1 year and annually thereafter	Cystoscopy at 3 months and annually thereafter	Cystoscopy at 3 months, 1 year and then discharge
Intermediate risk	Cystoscopy every 3 months for 2 years, then every 6 months for 2 years and annually thereafter	Cystoscopy every 3 months for 1 year, then 6 monthly for 2 years and annually thereafter	Escalating intervals up to 1 year, with cystoscopy at 3 months, 9 months, 18 months, 30 months and annually thereafter.
High risk	Cystoscopy every 3 months for 2 years, then every 6 months for 2 years and annually thereafter	Cystoscopy every 3 months for 2 years and annually thereafter	Cystoscopy every 3 months for 1 year, then 6 monthly for 1 year and annually thereafter

In addition to these variations, the use of a urinary biomarker (FISH) or cytology as a safety net to detect recurrences at the time points that would normally be checked under current practice was also considered. The diagnostic accuracy of these tests as well as cystoscopy were estimated using data from the systematic review of the clinical evidence conducted for this guideline, with most data being sourced from a systematic review by Mowatt et al. 2010.

Costs and utilities

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. GP visit). Where possible, all costs were estimated in 2012-13 prices.

The majority of costs were sourced from NHS reference costs 2012/13 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dosages from the British National Formulary (BNF) and unit cost information from the electronic market information tool (eMit). Where unit costs for drugs were not available from eMit, prices from the BNF were used. Resource use and cost information were obtained from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs were estimated by combining the life year estimates with utility values (or QOL weights) associated with being in a particular health state. These utility values were identified through a search of the available literature.

Base Case Results

The base case results of the analysis for are presented in the table below for patients in each risk category. The results are shown in the 'dominance rank' format as it allows for the best overall strategy to be evaluated.

Table 99: Base Case Cost-Effectiveness Result Using Dominance Rank

Follow-up strategy	Cost		QALYs		Cost per QALY
	Total	Incremental	Total	Incremental	
Low risk					
Reduced frequency	**£4,805**	**-**	**6.26**	**-**	**-**
Cytology w/ reduced frequency	£7,206	£2,401	6.29	0.0307	£78,310
FISH w/ reduced frequency	£8,024	£3,219	6.29	0.0383	£83,990
Slightly reduced frequency	£8,675	£3,869	6.29	0.0371	£104,392
Current practice	£8,845	£4,040	6.29	0.0381	£106,019
Intermediate risk					
Reduced frequency	**£17,037**	**-**	**6.15**	**-**	**-**
Cytology w/ reduced frequency	£18,998	£1,961	6.19	0.0420	£46,660
Slightly reduced frequency	£19,970	£2,933	6.18	0.0320	£91,762
FISH w/ reduced frequency	£20,531	£3,494	6.21	0.0560	£85,511
Cytology w/ slightly reduced frequency	£20,539	£3,502	6.19	0.0409	£62,574
FISH w/ slightly reduced frequency	£21,000	£3,962	6.20	0.0456	£86,845
Current practice	£21,988	£4,950	6.20	0.0454	£108,925
High risk					
Reduced frequency	£26,637	-	5.40	-	-
Cytology w/ reduced frequency	£26,903	£266	5.48	0.0720	£3,698
FISH w/ reduced frequency	**£27,112**	**£209**	**5.52**	**0.0409**	**£5,095**
Slightly reduced frequency	£27,227	£115	5.47	-0.0487	Dominated
Cytology w/ slightly reduced frequency	£27,362	£250	5.50	-0.0184	Dominated
FISH w/ slightly reduced frequency	£27,459	£347	5.52	-0.0009	Dominated
Current practice	£27,674	£563	5.52	-0.0016	Dominated

It can be seen that the optimal strategy in low and intermediate risk patients is the reduced frequency strategy. This strategy is the least effective of all the strategies but the difference is marginal and because it is substantially cheaper than the other strategies it was found to be cost-effective overall.

In the case of high risk patients, it can be seen that the reduced frequency strategy is again the cheapest strategy but it is no longer the preferred strategy in cost-effectiveness terms. Strategies of reduced frequency with a safety net using FISH or cytology were found to be more cost-effective than this strategy with the reduced frequency follow-up strategy with FISH found to be the most cost-effective (more cost-effective than cytology because of the superior sensitivity of FISH in the base case).

Sensitivity analysis

A series of one-way sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result.

The analyses showed that, in low and intermediate risk patients, reduced frequency follow-up was the most cost-effective strategy in all modelled scenarios. In the case of high risk patients, the optimal strategy remains the same as in the base case (i.e. reduced frequency with FISH) in the vast majority of the analyses. However, there are two exceptions where the reduced frequency follow-up becomes the most cost-effective strategy; one where the modelled time horizon is reduced to five years and another where the bladder cancer specific mortality rates are equivalent for NMIBC and MIBC patients.

The GDG were also interested in an analysis where only variations in follow-up frequency were considered (i.e. variations in diagnostic tests were excluded from the analysis). As in the full analysis, it was found that the optimal strategy in low and intermediate risk patients was the reduced frequency strategy. However, in the case of high risk patients, the cystoscopy frequency used in current practice was found to be the most cost-effective strategy with a cost per QALY of £9,487 in comparison to the next based strategy (Slightly reduced follow-up).

A probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case were replaced with values drawn from distributions around the mean values. It was found that, at a threshold of £20,000 per QALY, the reduced frequency follow-up strategy had a 98% and 91% probability of being cost-effective in the low and intermediate risk group, respectively. In high risk patients it was found that, at a threshold of £20,000 per QALY, the reduced follow-up strategy in combination with FISH had a 79% probability of being cost-effective.

Conclusion

The results of the analysis suggest that reducing the frequency of cystoscopic follow-up in low and intermediate risk patients is cost-effective. Furthermore, the results show that the addition of cytology or FISH as a safety net was not cost-effective in these risk groups. In high risk patients, the results of the analysis suggest that reducing cystoscopic follow-up alone is not cost-effective in comparison to current practice. However, the addition of cytology or FISH as a safety net was found to be cost-effective with a reduced frequency follow-up strategy with FISH found to be the most cost-effective strategy.

However, there are concerns about the lack of comparative data that investigates variations in follow-up and further research is required to fully assess the safety, effectiveness and cost-effectiveness of the proposed follow-up strategies.

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4 Managing muscle-invasive bladder cancer

4.1 The role of chemotherapy in treatment of organ confined muscle-invasive bladder cancer

5.1.1 Neoadjuvant chemotherapy

Review question: Which patients with bladder cancer should be offered neoadjuvant chemotherapy?

Rationale

Newly diagnosed bladder cancer covers a wide spectrum of disease states. Many patients' tumours can be successfully treated by relatively simple operations which do not necessitate removal of the bladder. In particular, those tumours which have not invaded the muscle of the bladder wall can usually be treated in this way. However some of these tumours do require more major surgery, such as complete removal of the bladder (cystectomy). Furthermore, if the tumour has invaded the muscle of the bladder wall, then there is a very high risk that the patient will die of bladder cancer without either cystectomy or intensive radiotherapy. Although cystectomy or radiotherapy offers the best chance of cure, unfortunately a significant proportion of these patients still go on to die of bladder cancer. This is usually due to the cancer returning either in the region of the bladder or, more typically, in other parts of the body such as the lungs, lymph nodes, liver or bones. For many cancers this risk of relapse can be reduced or delayed by giving drug treatments such as chemotherapy before and / or after surgery / radiotherapy. Two large trials have demonstrated that some patients with bladder cancer which has invaded the muscle wall undergoing either cystectomy or radiotherapy have better outcomes if they receive prior chemotherapy. However, this treatment is associated with significant side effects. These side effects may be more problematic in patients with other illnesses or patients who are generally less fit. At worst, the occurrence of side effects may prevent the patient from undergoing successful surgery or radiotherapy. Therefore careful selection of patients for this treatment is essential, or there is a real risk of doing more harm than good.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with MIBC undergoing radical treatment	Radical treatment alone Radical treatment plus neoadjuvant chemotherapy TURBT & neoadjuvant chemotherapy	Each other	• Overall survival • Disease-free survival • Metastases free survival • Treatment-related morbidity • Treatment-related mortality • Health-related quality of life, inc patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (SB).

Selection of studies

A relevant systematic review of randomised trials was published in 2004. For this evidence review, the search was updated and any trials published after the systematic review were selected.

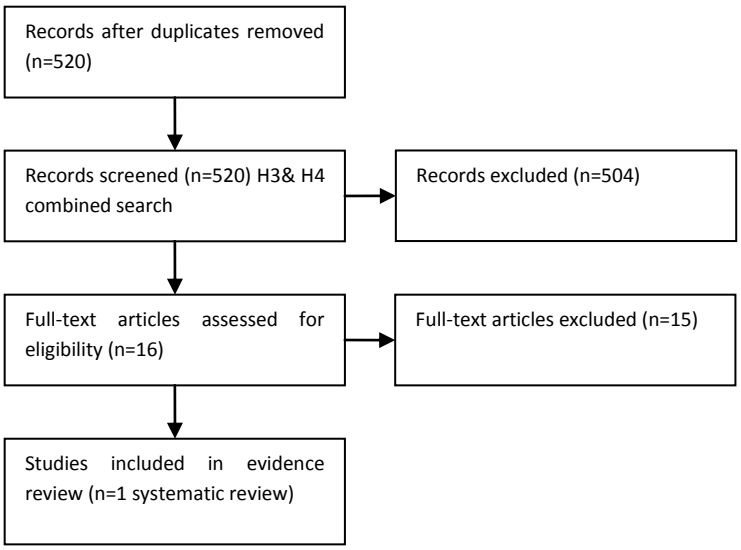
Data synthesis

Data from the systematic review were presented in forest plots using RevMan and stratified by chemotherapy type and treatment type as per the review.

RESULTS

Result of the literature searches

Figure 58. Study flow diagram



Study quality and results

No serious risk of bias in the included studies was reported in the systematic review. No further studies were identified from the literature search. The evidence from the systematic review is summarised in Table 100 and Figures 59-63.

Evidence statements

One systematic review and meta-analysis of individual patient data (3,005 patients from 11 randomised trials) was identified (Advanced Bladder Cancer Meta-Analysis Collaboration (ABC), 2004). No other randomised trials were identified. High quality evidence for overall survival came from 10 trials with a total of 2,809 patients. There is no clear evidence of statistical heterogeneity ($p=0.47$) or inconsistency between trials ($I^2=0\%$). All trials were reported to have adequate allocation concealment at randomisation. The pooled hazard ratio (HR) of 0.89 (95% CI 0.81 to 0.98) for these

trials represents an 11% relative reduction in the risk of death associated with neoadjuvant chemotherapy. This is equivalent to an absolute improvement of 4% at five years (95% CI 0% to 7%), increasing overall survival from 45% to 49%.

When trials were grouped by chemotherapy type there was no strong evidence that single-agent cisplatin had an effect on overall survival, as the 95% confidence interval of the effect estimate included the null value (HR 1.15, 95% CI 0.90 to 1.47). The pooled HR for trials using combination chemotherapy was 0.86 (95% CI 0.77 to 0.95), equivalent to a 14% relative reduction in the risk of death with neoadjuvant chemotherapy; an absolute benefit of 5% at five years (95% CI 2% to 9%), improving survival from 45% to 50%.

The trials of combination chemotherapy were grouped by planned local treatment: cystectomy alone, radical radiotherapy alone, or combined radiotherapy and cystectomy. There was no evidence of a difference in the effect of chemotherapy in the three local treatment groups (interaction p=0.656).

10 trials including 2,486 patients and 1,847 events (1,606 (87%) recurrences and 241 (13%) deaths) provided high quality evidence on disease-free survival, with a HR of 0.81 (95% CI 0.74 to 0.89) in favour of neoadjuvant chemotherapy. When grouped by chemotherapy type, moderate quality evidence from two trials showed that there was no effect of single-agent cisplatin on disease-free survival, as the 95% confidence intervals of the effect estimate included the null value (HR 1.14, 95% CI 0.83 to 1.55). The pooled HR for trials using combination chemotherapy was 0.78 (95% CI 0.71 to 0.86), equivalent to a 22% relative reduction in the risk of locoregional recurrence, metastases or death with neoadjuvant chemotherapy; an absolute disease-free survival benefit of 9% at five years (95% CI 5% to 12%).

For metastases-free survival, data from seven trials including 2,180 patients and 1,345 events were available. The numbers of events in each group were not provided in the systematic review. The pooled results for metastases-free survival shows a similar pattern to survival, both in terms of chemotherapy type and local treatment, with a significant benefit of platinum-based combination chemotherapy (HR 0.82, 95% CI 0.73 to 0.92); an absolute metastases-free survival benefit of 7% (95% CI 3% to 11%).

The systematic review states that there was insufficient data to formally investigate toxicity or health-related quality of life in these trials. However, where it was reported in the publications, the most common chemotherapy-related toxicities included nausea and vomiting, haematological toxicities, and impaired renal function.

Table 100. GRADE evidence profile: Neoadjuvant chemotherapy + radical treatment versus radical treatment alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant CT + local treatment	local treatment only	Relative (95% CI)	Absolute	
Overall survival											
10[1]	randomised trials	none	none	none	none	none	822/1406 (58.5%)	881/1420 (62%)	HR 0.89 (0.81 to 0.98)	4% (95% CI 0% to 7%) improvement of 5 yr survival from 45% to 49%	⊕⊕⊕⊕ HIGH
Overall survival by chemotherapy type - Single agent platinum											
3[1]	randomised trials	none	none	none	serious[2]	none	136/186 (73.1%)	137/207 (66.2%)	HR 1.15 (0.9 to 1.47)	5% (95% CI -14% to 4%) reduction of 5 yr survival	⊕⊕⊕O MODERATE
Overall survival by chemotherapy type - Platinum-based combination											
7[1]	randomised trials	none	none	none	none	none	686/1220 (56.2%)	744/1213 (61.3%)	HR 0.86 (0.77 to 0.95)	5% (95% CI 2% to 9%) improvement of 5 yr survival from 45% to 50%	⊕⊕⊕⊕ HIGH
Overall survival by treatment type											
7[1]	randomised trials	none	none	none	none	none	683/1214 (56.3%)	739/1207 (61.2%)	HR 0.86 (0.77 to 0.95)	-	⊕⊕⊕⊕ HIGH
Overall survival by treatment type - Cystectomy											
6[1]	randomised trials	none	none	none	none	none	413/762 (54.2%)	444/746 (59.5%)	HR 0.86 (0.75 to 0.98)	-	⊕⊕⊕⊕ HIGH
Overall survival by treatment type - Radiotherapy											
2[1]	randomised trials	none	none	none	serious[2]	none	184/263 (70%)	189/263 (71.9%)	HR 0.91 (0.74 to 1.11)	-	⊕⊕⊕O MODERATE
Overall survival by treatment type - Radiotherapy + cystectomy											
2[1]	randomised trials	none	none	none	serious[2]	none	86/189 (45.5%)	106/198 (53.5%)	HR 0.77 (0.58 to 1.02)	-	⊕⊕⊕O MODERATE
Disease-free survival											
10[1]	randomised trials	none	none	none	none	none	875/1419 (61.7%)	972/1427 (68.1%)	HR 0.81 (0.74 to 0.89)	8% improvement (95% CI 4% to 11%)	⊕⊕⊕⊕ HIGH
Disease-free survival by chemotherapy type - Single agent cisplatin											
2[1]	randomised trials	none	none	none	serious[2]	none	81/103 (78.6%)	85/114 (74.6%)	HR 1.14 (0.83 to 1.55)	5% reduction (95% CI -16% to 7%)	⊕⊕⊕O MODERATE
Disease-free survival by chemotherapy type - Platinum-based combination											
8[1]	randomised trials	none	none	none	none	none	794/1316 (60.3%)	887/1313 (67.6%)	HR 0.78 (0.71 to 0.86)	9% improvement of 5 yr survival (95% CI 5% to 12%)	⊕⊕⊕⊕ HIGH
Disease-free survival by treatment type - Cystectomy											
Not reported	randomised trials	none	none	none	none	none	Not reported	Not reported	HR 0.75 (0.66 to 0.84)	-	⊕⊕⊕⊕ HIGH

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant CT + local treatment	local treatment only	Relative (95% CI)	Absolute	
Disease-free survival by treatment type - Radiotherapy											
Not reported	randomised trials	none	none	none	serious[2]	none	Not reported	Not reported	HR 0.92 (0.76 to 1.11)	-	⊕⊕⊕O MODERATE
Disease-free survival by treatment type - Radiotherapy + cystectomy											
Not reported	randomised trials	none	none	none	none	none	Not reported	Not reported	HR 0.71 (0.54 to 0.94)	-	⊕⊕⊕⊕ HIGH
Metastases-free survival											
7[1]	randomised trials	none	none	none	none	none	Not reported	Not reported	HR 0.86 (0.77 to 0.95)	5% improvement (95% CI 2% to 9%)	⊕⊕⊕⊕ HIGH
Metastases-free survival by chemotherapy type - Single agent platinum											
Not reported[1]	randomised trials	none	none	none	serious[2]	none	Not reported	Not reported	HR 1.21 (0.88 to 1.67)	7% reduction (95% CI -18% to 5%)	⊕⊕⊕O MODERATE
Metastases-free survival by chemotherapy type - Platinum based combination											
Not reported[1]	randomised trials	none	none	none	serious[3]	none	Not reported	Not reported	HR 0.82 (0.73 to 0.92)	7% improvement (95% CI 3% to 11%)	⊕⊕⊕O MODERATE
Metastases-free survival by treatment type - Cystectomy											
Not reported[1]	randomised trials	none	none	none	serious[3]	none	Not reported	Not reported	HR 0.82 (0.70 to 0.96)	-	⊕⊕⊕O MODERATE
Metastases-free survival by treatment type - Radiotherapy											
Not reported[1]	randomised trials	none	none	none	serious[2]	none	Not reported	Not reported	HR 0.87 (0.71 to 1.06)	-	⊕⊕⊕O MODERATE
Metastases-free survival by treatment type - Radiotherapy + cystectomy											
Not reported[1]	randomised trials	none	none	none	serious[3]	none	Not reported	Not reported	HR 0.73 (0.56 to 0.97)	-	⊕⊕⊕O MODERATE
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Health related quality of life											
0	No evidence available										

[1] From Advanced Bladder Cancer Meta-Analysis Collaboration (ABC) systematic review (2004)

[2] Wide confidence interval (including null value) and/or low number of events limits the precision of this outcome

[3] Number of studies, events and participants not reported

Figure 59. Neoadjuvant CT + radical treatment vs. radical treatment alone. Outcome: Survival by chemotherapy type (ABC, 2004)

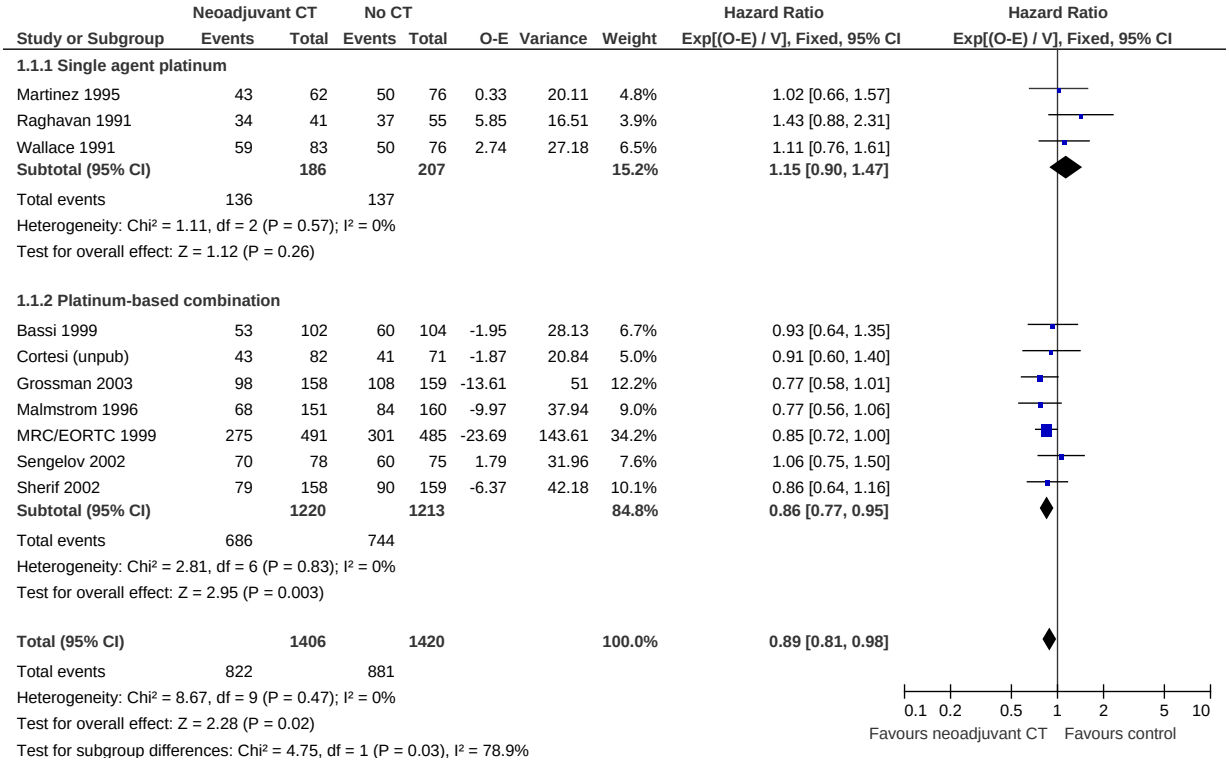


Figure 60. Neoadjuvant CT + radical treatment vs. radical treatment alone. Outcome: Survival by treatment type (combination CT trials only) (ABC, 2004)

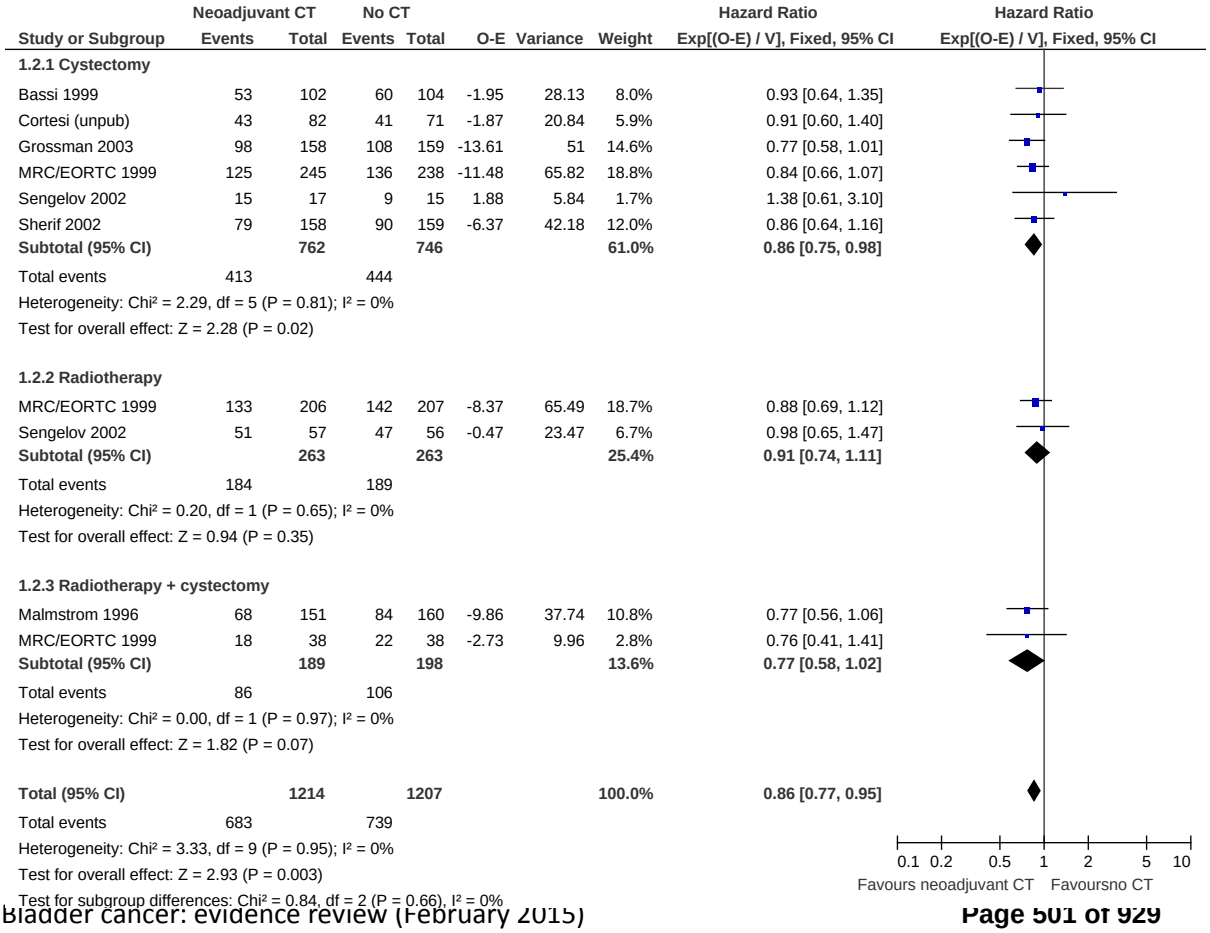


Figure 61. Neoadjuvant CT + radical treatment vs. radical treatment alone. Outcome: Disease-free survival by chemotherapy type (ABC, 2004)

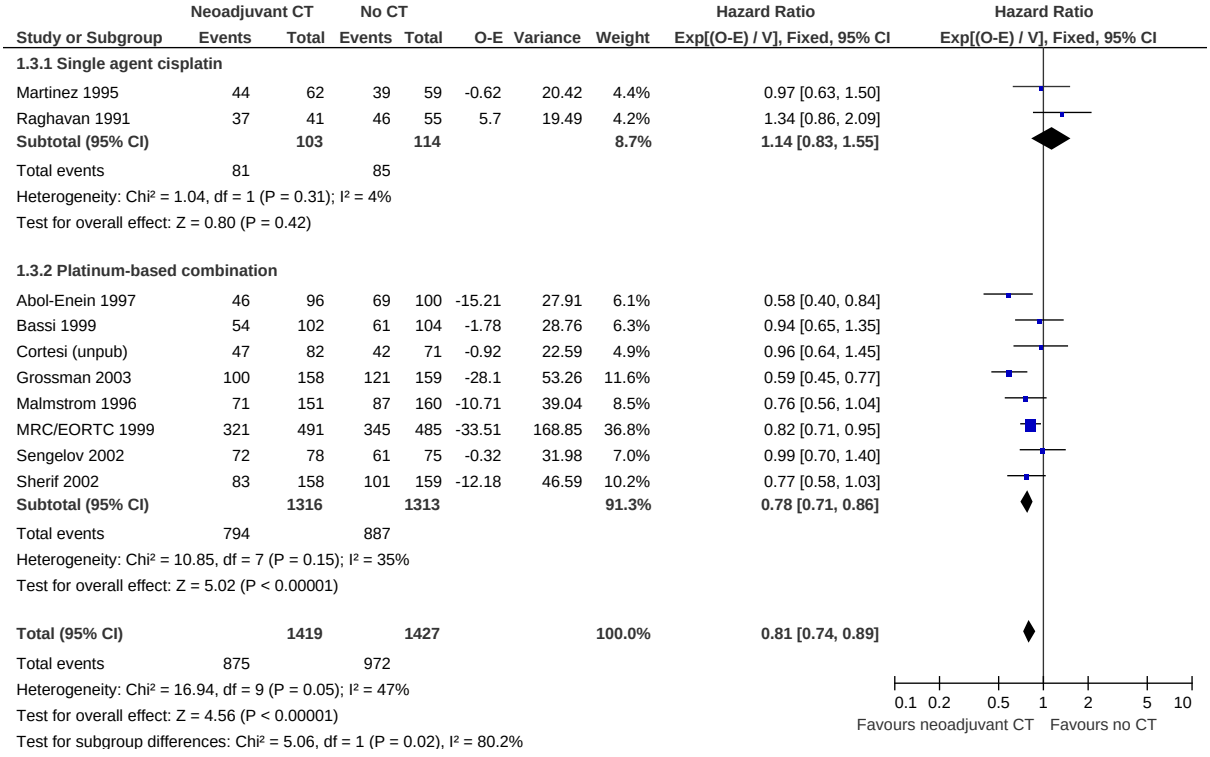


Figure 62. Concurrent CTRT + radical treatment vs. radical treatment alone. Outcome: Survival (ABC, 2004)

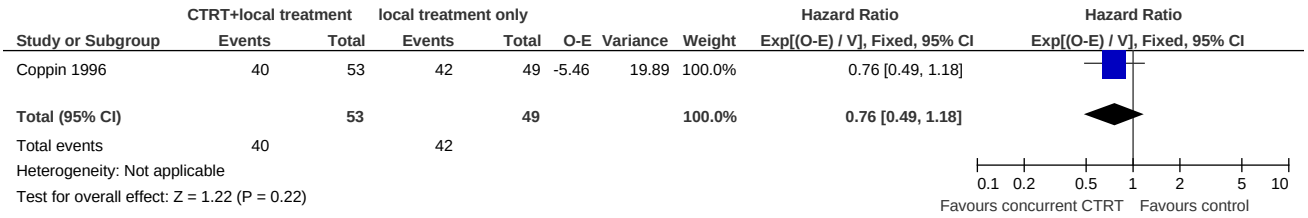
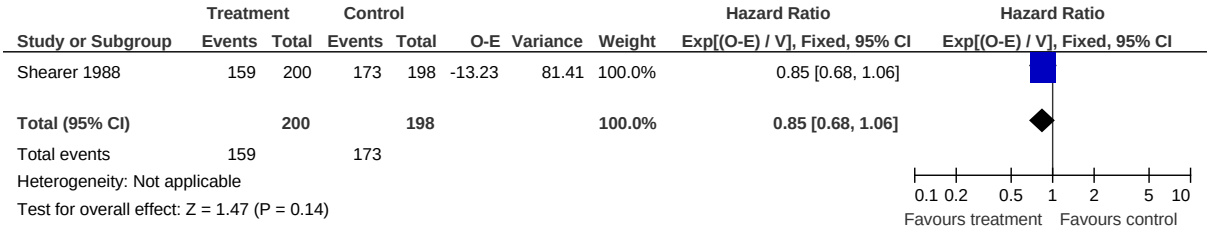


Figure 63. Neoadjuvant CT + radical treatment + adjuvant CT vs. radical treatment alone. Outcome: Survival (ABC, 2004)



References to included studies

Advanced Bladder Cancer (ABC) Overview Collaboration. Neoadjuvant chemotherapy for invasive bladder cancer. Cochrane Database of Systematic Reviews 2004; Issue 1, Art. No.: CD005246

References to excluded studies (with reasons for exclusion)

Reason: adjuvant chemotherapy

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. European Urology 2005; 48(2): 189-199.

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy for invasive bladder cancer (individual patient data). Cochrane Database of Systematic Reviews 2006;(2): CD006018

Lehmann, J et al. Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin in locally advanced bladder cancer: Results of a randomized, multicenter, phase III trial (AUO-AB 05/95). Journal of Clinical Oncology 2005; 23(22): 4963-4974.

Lehmann, J et al. Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. BJU International 2006; 97(1): 42-47.

Ruggeri, EM et al. Adjuvant chemotherapy in muscle-invasive bladder carcinoma: a pooled analysis from phase III studies. Cancer 2006; 106(4): 783-788.

Cognetti, F et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Annals of Oncology 2012; 23(3): 695-700.

Stadler, WM et al. Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011; 29(25): 3443-3449.

Leow JJ, et al. Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials. European Urology (2013)

Reason: duplicate of Cochrane review

Vale, CL. Neoadjuvant chemotherapy in invasive bladder cancer: Update of a systematic review and meta-analysis of individual patient data. European Urology 2005; 48(2): 202-205.

Reason: included in Cochrane review

Sherif, A et al. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. European Urology 2004; 45(3): 297-303.

International Collaboration of Trialists et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. Journal of Clinical Oncology 2011; 29(16): 2171-2177.

Reason: superseded by Cochrane review (similar conclusions)

Winquist, E et al. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. [Review] [66 refs]. Journal of Urology 2004; 171(2:Pt 1): t-9.

Reason: secondary analysis of trial included in Cochrane review

Scosyrev, E et al. Do mixed histological features affect survival benefit from neoadjuvant platinum-based combination chemotherapy in patients with locally advanced bladder cancer? A secondary analysis of Southwest Oncology Group-Directed Intergroup Study (S8710). BJU International 2011; 108(5): 693-699.

Reason: no meta-analysis, for info only

Meeks, JJ et al. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. [Review]. European Urology 2012; 62(3): 523-533.

Sternberg, CN et al. ICUD-EAU International Consultation on Bladder Cancer 2012: chemotherapy for urothelial carcinoma-neoadjuvant and adjuvant settings. European Urology 2013; 63(1): 58-66.

Evidence tables

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding	Additional comments
Advanced bladder cancer meta-analysis collaboration (2004)	Cochrane systematic review of randomised trials (individual patient data)	3005 from 11 trials of neoadjuvant chemotherapy, published 1991-2003 (unpublished data from Cortesi)	See Table 1. Meta-analysis represents 98% of individuals from all known eligible randomised trials.	6 trials of cystectomy, 2 trials radiotherapy, 1 trial pre-operative radiotherapy and cystectomy. 2 trials used a combination of one or more local treatment. All used platinum-based chemotherapy. 10 trials used cisplatin as either single agent or in combination with one or more of doxorubicin/epirubicin, methotrexate and vinblastine. Cisplatin dose range from 70mg/m^2 per cycle for 2-4 cycles to 100mg/m^2 per cycle given in 2-3 cycles, every 2-4 weeks. One trial (Abol-Enein) used carboplatin with methotrexate and vinblastine	Radical treatment alone	Median =6.4 years	Overall survival at 5-years Disease-free survival Metastases-free survival Loco-regional disease-free survival	BMRC	Systematic review methodology and risk of bias assessment

4.1.2 Adjuvant chemotherapy

Review question: Which patients with bladder cancer should be offered adjuvant chemotherapy?

Rationale

Muscle invasive bladder cancer (MIBC) is usually treated locally by radiotherapy and surgery. However the average 5 year survival for patients with MIBC is in the order of 50-60%. Patients dying of MIBC most commonly do so following the development of metastatic (cancer at distant sites) disease. It is, thus, logical to consider that to significantly improve the prognosis it will be necessary to reduce the incidence of the development of metastatic disease.

It is theorised that chemotherapy may be more likely to eradicate this metastatic disease when subclinical and thus reduce metastatic relapse and improve survival. Neo-adjuvant or adjuvant chemotherapy (chemotherapy given before [neo-adjuvant] or after [adjuvant] local treatment in patients with no clinically evident metastatic disease) has been shown to improve survival at a number of cancer sites (e.g. Breast cancer, Colorectal cancer).

A number of trials have been conducted in bladder cancer of both neo-adjuvant and adjuvant chemotherapy that have been suggestive of benefit. Clinical implementation has been mixed. For example, studies in US have suggested <10-20% of MIBC patients are receiving (neo) adjuvant chemotherapy and there remains disagreements over whether neo adjuvant or adjuvant therapy should be offered to all suitable patients or selected patients.

Thus, do these studies provide convincing evidence of survival benefit? If so is there evidence that any groups of patients benefit more than others or should treatment be offered to all patients with localised MIBC? Are there selection criteria or contra-indications for adjuvant chemotherapy? Is there any evidence as to whether it better to use neo-adjuvant chemotherapy or use adjuvant chemotherapy for all or selected cases? What are the risk of this therapy? Do the risks outweigh benefit for some patients? Are there any recommendations on type of chemotherapy?

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with MIBC undergoing radical treatment	Radical treatment plus adjuvant chemotherapy	Radical treatment alone	• Overall survival • Disease-free survival • Metastases free survival • Treatment-related morbidity • Treatment-related mortality • Health-related quality of life, inc patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (SB).

Selection of studies

A relevant systematic review of randomised trials was published in 2006 and was subsequently updated in 2013. For this evidence review, the search was updated and any trials published after the systematic review were selected.

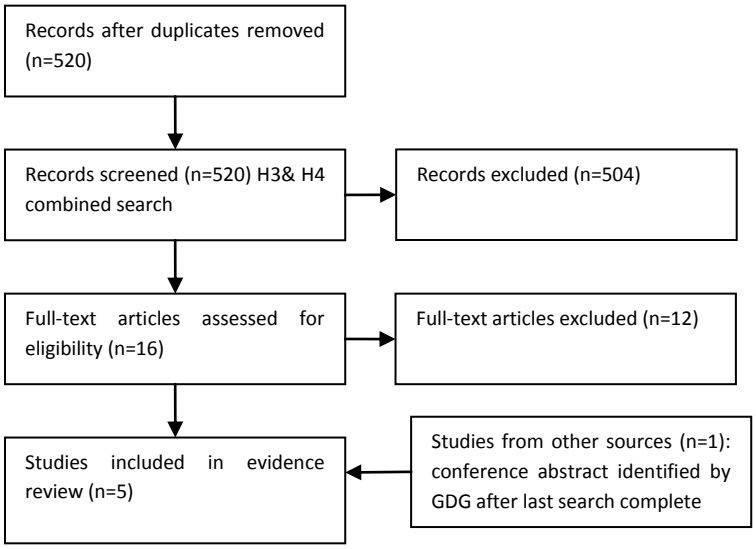
Data synthesis

Data from the systematic review and one further trial (published as an abstract only) were presented in forest plots using RevMan and stratified by chemotherapy type as per the review.

RESULTS

Result of the literature searches

Figure 64. Study flow diagram



Study quality and results

One systematic review of randomised trials (Leow *et al.*, 2013) and one further trial which was published as a conference abstract only, were included in the evidence review. For the outcome of metastases-free survival, evidence was obtained from the 2006 Cochrane review. Treatment-related morbidity data came from two trials included in the systematic review. Study quality and results are summarised in Table 83 and Figures 65-67.

Evidence statements

Overall survival

One systematic review and meta-analysis of nine randomised trials including 945 patients, reported a pooled hazard ratio (HR) for overall survival of 0.77 (95% CI 0.59 to 1.00) (Leow *et al.*, 2013). The addition of data from 284 patients from the EORTC trial (Sternberg *et al.*, 2014) provided a pooled HR of 0.77 (95% CI 0.62 to 0.96) in favour of adjuvant chemotherapy, equivalent to a 23% relative decrease in the risk of death with local treatment and adjuvant chemotherapy compared to local treatment alone (moderate quality evidence).

In an analysis of trials based on the type of chemotherapy used, the HR for one trial with only 45 events that used single-agent cisplatin was 1.02 (95% CI 0.57 to 1.84), suggesting uncertainty about the effect of adjuvant chemotherapy on overall survival. For the seven trials that used cisplatin-based combination chemotherapy, the pooled HR was 0.75 (95% CI 0.62 to 0.91), representing a 26% relative decrease in the risk of death on chemotherapy compared to that on control (moderate quality evidence). For two trials using gemcitabine-cisplatin combination chemotherapy the pooled HR was 0.71 (95% CI 0.21 to 2.35), with wide confidence intervals suggesting uncertainty about the effect of adjuvant chemotherapy on overall survival (low quality evidence).

Disease-free survival

A meta-analysis of nine trials including 1,106 patients provided an overall HR of 0.64 (95% CI 0.49 to 0.85), representing a 36% relative decrease in the risk of recurrence or death on chemotherapy compared to that on control. However, a moderate amount of between-trial heterogeneity or inconsistency was identified between the trials (p=0.007; I^2=62%) (low quality evidence). For the six trials (690 patients) that used cisplatin-based combination chemotherapy the HR was 0.60 (95% CI 0.47 to 0.75), representing a 40% relative decrease in the risk of recurrence or death on chemotherapy compared to that on control (moderate quality evidence).

Metastases-free survival

Low quality evidence from the Advanced Bladder Cancer (ABC, 2006) meta-analysis reported that only two trials of 192 patients with 115 events provided data for metastases-free survival. This analysis was therefore extremely limited due to the low number of patients and was not presented.

Treatment-related morbidity

Treatment-related morbidity was not reported in the existing meta-analyses. Cognetti *et al.* (2012) provided low quality evidence on toxicities resulting from adjuvant gemcitabine and cisplatin therapy. Out of the 89 patients who received adjuvant chemotherapy 28.1% experienced grade three or four neutropenia, 14.6% experienced grade three or four thrombocytopenia, and 12.4% experienced grade three or four leukopenia. These were the most common toxicities reported. In the trial by Lehmann *et al.* (2006), three patients in the MVAC/MVEC chemotherapy arm had severe and recurrent vomiting. None of the patients had loss of renal function.

Treatment-related mortality

Treatment-related mortality was not reported in the existing meta-analyses. Cognetti *et al.* (2012) reported that there were no drug toxicity-related deaths. There was one death due to treatment toxicity in the immediate adjuvant chemotherapy arm in one trial (Sternberg *et al.*, 2014).

Health-related quality of life

Quality of life was not reported in the existing meta-analyses. Cognetti *et al.* (2012) provided low quality evidence that global quality of life was similar for patients in both arms of the trial. In the adjuvant chemotherapy arm there was a slight worsening of general quality of life during the last two months of chemotherapy, which improved during follow-up and was then comparable to the control group (number of patients and mean values not reported).

Table 101. GRADE evidence profile: Adjuvant chemotherapy + radical treatment verses radical treatment alone (or deferred chemotherapy)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant CT + local treatment	local treatment alone	Relative (95% CI)	Absolute	
Overall survival											
10[1]	randomised trials	serious[2]	none	none	none	none	287/616 (46.6%)	346/613 (56.4%)	HR 0.77 (0.62 to 96)	92 fewer per 1000 (from 15 fewer to 162 fewer)	⊕⊕⊕O MODERATE
Overall survival - Single agent Cisplatin											
1[1]	randomised trials	serious[2]	none	none	serious[3,4]	none	23/46 (50%)	22/45 (48.9%)	HR 1.02 (0.57 to 1.84)	7 more per 1000 (from 171 fewer to 220 more)	⊕⊕OO LOW
Overall survival - Cisplatin-based combination											
7[1]	randomised trials	serious[2]	none	none	none	none	194/400 (48.5%)	241/402 (60%)	HR 0.75 (0.62 to 0.91)	103 fewer per 1000 (from 34 fewer to 167 fewer)	⊕⊕⊕O MODERATE
Overall survival - Gemcitabine-Cisplatin combinations											
2[1]	randomised trials	serious[2]	serious[5]	none	serious[3,4]	none	70/170 (41.2%)	83/166 (50%)	HR 0.71 (0.21 to 2.33)	111 fewer per 1000 (from 365 fewer to 301 more)	⊕OOO VERY LOW
Disease-free survival											
8[1]	randomised trials	serious[2]	serious[5]	none	none	none	270/555 (48.6%)	337/551 (61.2%)	HR 0.64 (0.49 to 0.85)	158 fewer per 1000 (from 59 fewer to 241 fewer)	⊕⊕OO LOW
Disease-free survival - Single agent Cisplatin											
1[1]	randomised trials	serious[2]	none	none	serious[3,4]	none	24/46 (52.2%)	23/45 (51.1%)	HR 1.02 (0.58 to 1.8)	7 more per 1000 (from 171 fewer to 213 more)	⊕⊕OO LOW
Disease-free survival - Cisplatin based combination											
6[1]	randomised trials	serious[2]	none	none	none	none	173/344 (50.3%)	220/346 (63.6%)	HR 0.60 (0.47 to 0.75)	181 fewer per 1000 (from 258 fewer to 364 fewer)	⊕⊕⊕O MODERATE
Disease-free survival - Gemcitabine-Cisplatin combinations											
2[1]	randomised trials	serious[2]	serious[5]	none	serious[3,4]	none	73/165 (44.2%)	94/160 (58.8%)	HR 0.64 (0.23 to 1.79)	155 fewer per 1000 (from 403 fewer to 208 more)	⊕⊕OO LOW
Metastases-free survival											
2[6]	randomised trials						115/192				
Grade 3-4 Thrombocytopenia (assessed with: WHO grading system)											
1[7]	randomised trials	serious[8]	none	none	serious[4]	none	13/89 (14.6%)	-	-	-	⊕⊕OO LOW
Grade 3-4 Neutropenia (assessed with: WHO grading system)											
1[7]	randomised trials	serious[8]	none	none	serious[4]	none	25/89 (28.1%)	-	-	-	⊕⊕OO LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant CT + local treatment	local treatment alone	Relative (95% CI)	Absolute	
Grade 3-4 Leukopenia (assessed with: WHO grading system)											
1[7]	randomised trials	serious[8]	none	none	serious[4]	none	11/89 (12.4%)	-	-	-	⊕⊕OO LOW
Severe vomiting											
1[9]	randomised trials	serious[10]	none	none	serious[4]	none	3/21 (14.3%)	-	-	-	⊕⊕OO LOW
Treatment-related mortality											
2[11]	randomised trials	serious[8]	none	none	serious[4]	none	1/230 (0.4%)	-	-	-	⊕⊕OO LOW
Health related quality of life											
1[7]	randomised trials	serious[8,12]	none	none	serious[4]	none	-	-	-	Values not reported. QoL similar in both arms.	⊕⊕OO LOW

[1] As reported in systematic review by Leow et al (2013) and the addition of data from Sternberg (2014)

[2] All trials were non double-blinded or open-label trials. Individual patient data not available for 3 trials. Many studies closed early due to poor accrual or low benefit. In two trials (Lehmann 2006; Skinner 1990) around 25% of patients randomised to chemotherapy did not receive it; many received no therapy at all or received regimens other than in the trial protocol. Four trials (Lehmann, 2006; Skinner 1990; Freiha 1996; Bono 1997) did not specify salvage chemotherapy for patients on the control arm whose disease progressed or recurred. For Sternberg (2014) only a conference abstract was available so study quality could not be assessed. The HR for progression-free survival was calculated from number of events and p value assuming randomisation ratio of 1:1

[3] Wide confidence interval (includes null effect) limits the precision of this outcome

[4] Low number of events limits precision of outcome

[5] Significant statistical heterogeneity present.

[6] As reported in Cochrane meta-analysis (ABC, 2006) - Data on metastases-free survival were only available for 2 trials including 192 patients and 115 events and were therefore not presented in the Cochrane meta-analysis

[7] Cognetti (2012)

[8] Non-blinded study. Study closed early for low accrual. IPD not available.

[9] Lehmann (2006)

[10] No blinding reported. Trial stopped early for benefit.

[11] Cognetti (2012); Sternberg (2014)

[11] Mean QoL values and number of respondents not reported

Figure 65. Adjuvant CT + radical treatment vs. radical treatment alone

Outcome: Overall survival by chemotherapy type (Leow, 2013 plus Sternberg, 2014)

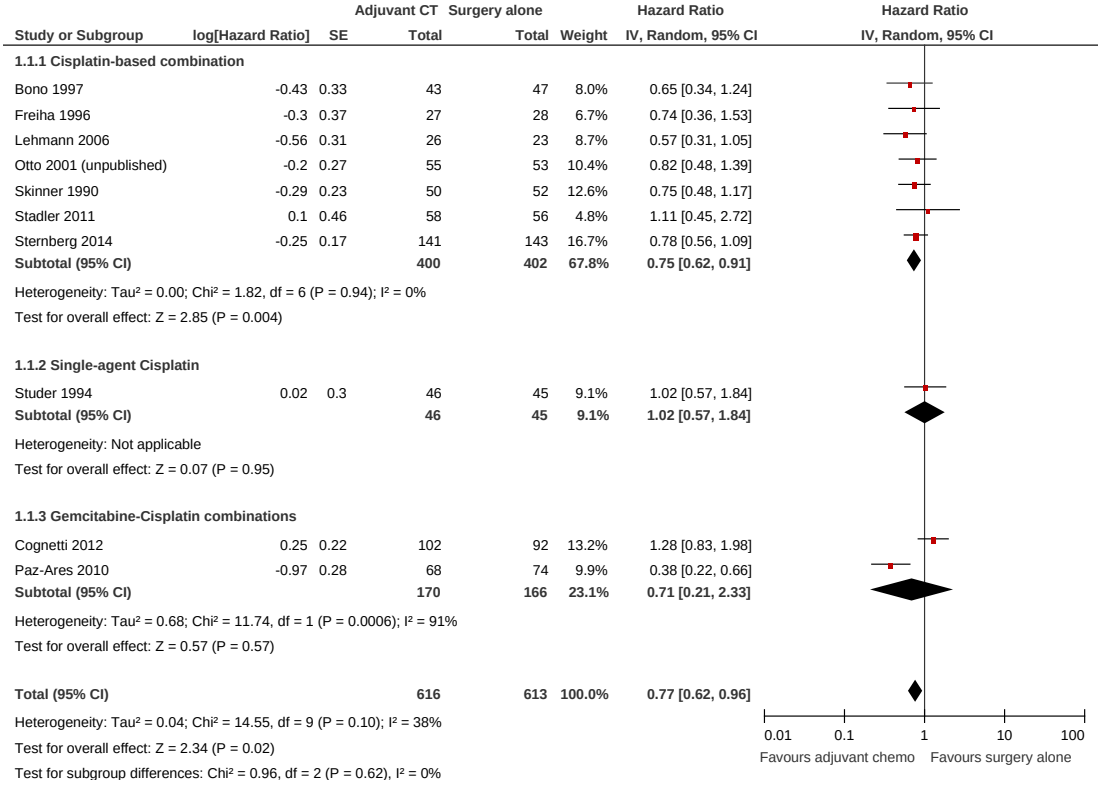


Figure 66. Adjuvant CT + radical treatment vs. radical treatment alone

Outcome: Disease-free survival by chemotherapy type (Leow, 2013 plus Sternberg, 2014).

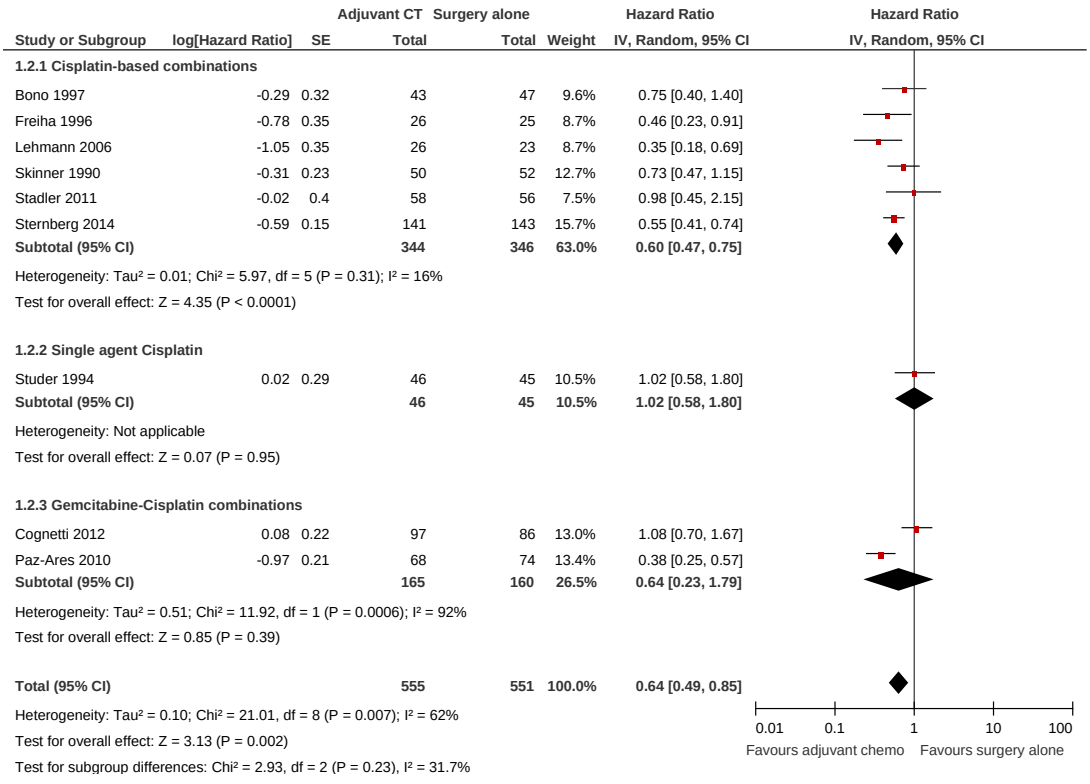
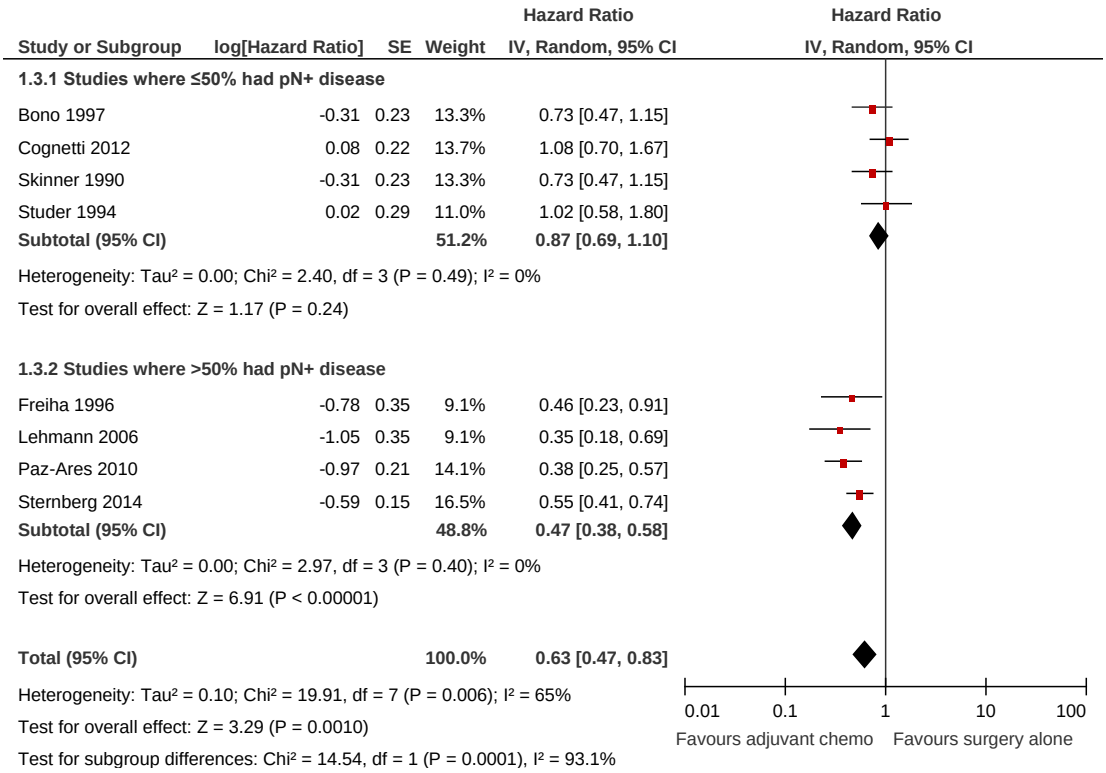


Figure 67. Adjuvant CT + radical treatment vs. radical treatment alone. Outcome: Disease-free survival by nodal status (Leow, 2013 plus Sternberg, 2014)



References to included studies

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy for invasive bladder cancer (individual patient data). Cochrane Database of Systematic Reviews 2006; Issue 2, Art. No.: CD006018.

Cognetti, F et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Annals of Oncology 2012; 23(3): 695-700.

Lehmann, J et al. Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. BJU International 2006; 97(1): 42-47.

Leow JJ, et al. Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials. European Urology 2014; 66(1): 42-54

Sternberg, CN et al. Final results of EORTC intergroup randomized phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3T4 and/or N+ M0 transitional cell carcinoma (TCC) of the bladder. Journal of Clinical Oncology 2014; 32(5s): abstract 4500

References to excluded studies (with reasons for exclusion)

Reason: duplicate publication of Cochrane review

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. European Urology 2005; 48(2): 189-199.

Reason: neoadjuvant chemotherapy

Advanced Bladder Cancer Overview Collaboration. Neoadjuvant chemotherapy for invasive bladder cancer. [Review] [37 refs]. Cochrane Database of Systematic Reviews.(2):CD005246, 2005. 2005;(2): CD005246

Vale, CL. Neoadjuvant chemotherapy in invasive bladder cancer: Update of a systematic review and meta-analysis of individual patient data. European Urology 2005; 48(2): 202-205.

Sherif, A et al. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. European Urology 2004; 45(3): 297-303.

Winquist, E et al. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. [Review] [66 refs]. Journal of Urology 2004; 171(2:Pt 1): t-9.

International Collaboration of Trialists et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. Journal of Clinical Oncology 2011; 29(16): 2171-2177.

Scosyrev, E et al. Do mixed histological features affect survival benefit from neoadjuvant platinum-based combination chemotherapy in patients with locally advanced bladder cancer? A secondary analysis of Southwest Oncology Group-Directed Intergroup Study (S8710). BJU International 2011; 108(5): 693-699.

Reason: comparison not relevant to PICO (no local treatment only group)

Lehmann, J et al. Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin in locally advanced bladder cancer: Results of a randomized, multicenter, phase III trial (AUO-AB 05/95). Journal of Clinical Oncology 2005; 23(22): 4963-4974.

Reason: superseded by Cochrane and Leow (2013) review

Ruggeri, EM et al. Adjuvant chemotherapy in muscle-invasive bladder carcinoma: a pooled analysis from phase III studies. Cancer 2006; 106(4): 783-788.

Reason: no meta-analysis, for info only

Meeks, JJ et al. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. [Review]. European Urology 2012; 62(3): 523-533.

Sternberg, CN et al. ICUD-EAU International Consultation on Bladder Cancer 2012: chemotherapy for urothelial carcinoma-neoadjuvant and adjuvant settings. European Urology 2013; 63(1): 58-66.

Reason: included in systematic review (Leow, 2013) other outcomes not reported

Stadler, WM et al. Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011; 29(25): 3443-3449.

Evidence tables

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Leow et al (2013	Systematic review and meta-analysis	945 patients from 9 trials of adjuvant chemotherapy	Patients with biopsy-proven, muscle-invasive (clinical stage T2–T4a) transitional cell carcinoma of the bladder. Trials that also included a minority of pT1 patients were also included.	Experimental group received local definitive treatment (resection) with adjuvant cisplatin-based chemotherapy. The same local treatment used as in control arm.	Control group received local treatment (same as experimental group) without adjuvant chemotherapy. Controls must not have received any neoadjuvant chemotherapy.	Not reported	Overall survival (time from study initiation until death/censoring). HR 0.77 (0.59-0.99) Disease-free survival (time from initiation until first recurrence or progression or death). HR 0.66 (0.45-0.91). Death is defined as death by any cause.	None	Update of ABC meta-analysis. Systematic review methodology and risk of bias assessment Random effects analysis and sensitivity analysis performed.
Advanced bladder cancer meta-analysis collaboration (2006)	Cochrane systematic review of randomised trials (individual patient data) published 1990-1997	491 from 6 trials of adjuvant chemotherapy, (unpublished data from Otto)	Meta-analysis represents 90% of all patients randomised in adjuvant cisplatin-based chemotherapy trials.	In all trials the planned local treatment was cystectomy and all trials used cisplatin-based chemotherapy; one as a single agent and five in combination with one or more of methotrexate, vinblastine, cyclophosphamide, and either doxorubicin or epirubicin. The planned cisplatin doses ranged from 90mg/m^2 per cycle for 2 cycles to 100mg/m^2 per cycle for 4 cycles, every 3-4 weeks. Four of the 6 cycles stopped early; three because the results of the interim analysis favoured chemotherapy and the fourth because the interim results showed less benefit of chemotherapy than	Radical treatment alone	Median =5.2 years (range 0.1 to 14.8)	Overall survival- HR 0.75 (0.60-0.96) Disease-free survival- HR 0.68 (0.52-0.88) Metastases-free survival (effect size not reported) Loco-regional disease-free survival (effect size not reported)	BMRC	

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
				anticipated.					
Cognetti 2012	Randomised trial 2001-2007	194 allocated to control (n=92) or 4 courses of adjuvant CT (n=102). 183 included in final analysis.	1. Histologically proven TCC 2. pT2G3(N0–2),or pT3–4(N0–2) any G, or pN1–2, any T , any G 3. Radical cystectomy performed with no residual disease and minimum of 10 lymph nodes dissected 4.Randomization within 10wk after surgery 5. ECOG PS≤2 6. Age ≤75 yr 7.Adequate bone marrow reserve 8. Creatinine clearance ≥60 ml/min 9. Good liver function 47.5% pN+	After cystectomy, patients in the adjuvant CT arm were further assigned to receive 2 schedules of the same regimen of gemcitabine plus cisplatin. Cycles were repeated every 28 days for 4 cycles. Median time to therapy was 8 weeks (range 4 to 12 weeks). Only 62% could complete CT as planned	Observation after cystectomy and treatment on relapse	Median 35 months (IQR 15-57)	Over survival HR 1.29 (0.84-1.99) Disease-free survival HR 1.08 (0.73-1.59) Toxicity QoL similar for control and adjuvant CT arms	Italian minister of health	Trial stopped early due to low accrual (11 patients were lost after randomisation (6 control, 5 treatment) and were not considered assessable in final analysis. 8 patients randomised to the treatment arm did not start chemotherapy and were not included in the toxicity analysis)
Lehmann 2006	Randomised trial 1987-1990	26 in treatment arm, 23 control arm	Radical cystectomy patients with histologically confirmed locally advanced bladder cancer Tumor stages pT3,pT4a, and/or pN+ using 2002 TNM system 41 male, 8 female, 59% pN0	MVAC or MVEC (one patient received carboplatin instead of cisplatin). 3 cycles	Radical treatment alone	Median 160 months	Overall survival HR 0.57 (95% CI 0.31 to 1.05) Progression-free survival HR 0.35 (95% CI 0.18 to 0.69)		44% of control arm received systemic chemo on progression. Trial stopped early because interim analysis showed advantage for adjuvant chemo

Study	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Sternberg 2014	Randomised phase III trial 2002-2008	284	Pt characteristics were well balanced in the treatment groups; median age was 61 yrs with similar pT and nodal status (70% N+). Most received GC.	Immediate adjuvant chemotherapy: Within 90 days after cystectomy, pts were randomized to 4 cycles of GC, HD-MVAC or MVAC adjuvant chemotherapy.	Deferred adjuvant chemotherapy: 6 cycles of deferred chemotherapy at relapse	Median and maximum f/u is 7.0 and 10.4 yrs in the immediate and 7.2 and 10.6 yrs in the deferred arm	Main endpoint was OS with PFS a secondary endpoint. 176 pts (62.0%) progressed or died, 73 (51.8%) on the immediate and 103 (72.0%) on the deferred arm. Median and 5 yr PFS are 2.9 yrs and 46.8% on the immediate and 0.9 yrs and 29.5% on the deferred arm (p< 0.0001). 148 pts (52.1%) died, 66 (46.8%) on the immediate and 82 (57.3%) on the deferred arm. Median and 5 yr OS are 6.8 yrs and 53.6% on the immediate and 4.6 yrs and 47.7% on the deferred arm, HR=0.78 (95.09% CI: 0.56, 1.10, p=0.13). Grade 3/4 AEs in the immediate arm included myelosuppression (26%), neutropenia (38%) and thrombocytopenia (28%). One pt died due to toxicity in the immediate arm.	Not reported	Abstract only. Unable to assess study quality. Trial closed for poor accrual. Leow meta-analysis updated for overall survival and disease-free survival HR for progression-free survival calculated from number of events and p value assuming randomisation ratio of 1:1

4.2 Treatment of organ confined muscle-invasive bladder cancer

5.2.1 Radical cystectomy versus radical radiotherapy

Review question: In which patient groups with muscle invasive bladder cancer would radical cystectomy produce better outcomes than radical radiotherapy and in which groups would radical radiotherapy produce better outcomes?

Rationale

About a quarter of all bladder cancer patients have cancer in the muscle coat of the bladder (muscle invasive bladder cancer, or MIBC). This has a high risk of spread and presents an immediate threat to life. We know that when surgery is done to remove the bladder (cystectomy) because of MIBC, in about 20 to 25 % of patients, there is microscopic evidence of spread to the lymph glands at this stage, implying that the same level of risk of lymph gland involvement may be the case for all patients with MIBC. Spread to the lymph glands usually reduces the chance of cure sharply. This is the basis of the immediate threat in MIBC.

The two treatment options are cystectomy and radiotherapy. We do not have high quality evidence to compare their benefits, so we do not know for sure which is the more effective treatment for MIBC. We do know that cystectomy has a far greater impact on patients than does radiotherapy, meaning a much harder treatment to cope with and a far higher likelihood of significant side-effects. In many countries at present, including the UK, there is a view that the chance of cure may be higher with cystectomy than radiotherapy, and this is the justification for the common recommendation of cystectomy rather than radiotherapy, despite the higher risk of side-effects.

There are believed to be some adverse factors for surgery and some adverse factors for radiotherapy. Being frail or elderly, having other serious medical conditions, or not having sufficient mental capacity to be able to participate actively in recovery from cystectomy are regarded as adverse factors for surgery. Some factors, conversely, are regarded as adverse for radiotherapy: these include previous pelvic radiotherapy, certain bowel disorders (inflammatory bowel disease), significant previous pelvic surgery (that might result in adhesions with bowel stuck to the bladder), and some factors related to the tumour, such as obstruction to one or both kidneys, or carcinoma in situ.

Given that the treatments differ so much in terms of their impact, it is crucial to identify those patients who would have better outcomes with surgery than with radiotherapy, and vice versa.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with diagnosed (non metastatic M0) MIBC <u>Subgroups:</u> - Performance status - Patient age - Gender - Co morbid disease (renal	Radical cystectomy Radical radiotherapy (inc. Chemo-radiation) Radical cystectomy & Radical radiotherapy	Each other	• Overall survival • Disease-free survival • Metastases free survival • Treatment-related morbidity

failure) - Previous treatment - Tumour characteristics (variant urothelial histology, non urothelial, presence of concomitant carcinoma in situ, T-stage, N-stage) - Hydronephrosis			• Treatment-related mortality • Health-related quality of life inc, patient reported outcomes • Subsequent treatment

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

After discussion with the GDG it was decided that studies of neoadjuvant radiotherapy plus cystectomy versus cystectomy alone where patients were treated prior to 1990 should be excluded as radical treatments have changed since then, and these studies would not be relevant to current practice. Only comparative studies were selected at first, but it was considered relevant by the GDG to also include large series (>100 patients) of combined multi-modality therapy and large recent cystectomy series (>1000 patients, comparable to UK practice).

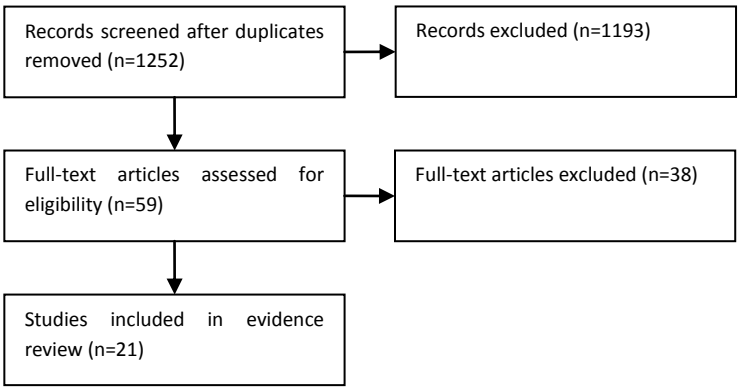
Data synthesis

Data was extracted into GRADE and risk ratios were calculated using RevMan where possible.

RESULTS

Result of the literature searches

Figure 68. Study flow diagram



Study quality and results

Evidence was provided by one systematic review of randomised trials. Six comparative observational studies of cystectomy versus radiotherapy, three large cystectomy series, and four large series of multimodality therapy were also included. Evidence is summarised in Tables 102-107.

Evidence statements

Low quality evidence from one systematic review of three randomised trials (439 patients) suggests that pre-operative radiotherapy followed by radical cystectomy (surgery) is favoured over radical radiotherapy with salvage cystectomy (radiotherapy) in terms of overall survival at three years (OR 1.91, 95% CI 1.30 to 2.87) and at five years (OR 1.87, 95% CI 1.22 to 2.87). Overall survival at three years was 45% for surgery and 28% for radiotherapy, giving an absolute improvement of 16%. One trial reported low quality evidence of disease-specific survival with an odds ratios in favour of surgery but not statistically significant at three years (OR 1.66, 95% CI 0.92 to 2.99) and five years (OR 1.39, 95% CI 0.75 to 2.57).

Six comparative observational studies (4,328 patients) provided very low quality of overall survival at five years, which ranged from 37% to 53% across studies for cystectomy and from 21% to 68% for radiotherapy. Five out of the six studies reported no significant difference between treatments in terms of overall survival. One study of 10,807 patients provided low quality evidence suggesting an overall survival advantage for those who had radical cystectomy compared to bladder preserving therapy (including radiotherapy) in all age groups. The survival benefit was smaller for patients over 79 years old (18 months versus 15 months) although the 95% confidence intervals still suggest a significant difference in favour of surgery (HR 1.32, 95% 1.19 to 1.46). In four series of bladder trimodality therapy (TURBT + chemoradiotherapy), five-year overall survival ranged from 51% to 68%, which compares to 58% in one large cystectomy series of 1100 patients.

Five comparative observational studies reported very low quality evidence of five-year disease-specific survival, with none of the studies reporting a significant difference between radical cystectomy (53% to 67%) and radiotherapy (48% to 75%). In three large cystectomy series, five-year disease-specific survival ranged from 65% to 76%. One study of 10,807 patients provided low quality evidence suggesting an advantage in disease-specific survival for those who had radical cystectomy compared to bladder preserving therapy (including radiotherapy) in all age groups.

One study of 141 patients with T2N0M0 bladder cancer provided very low quality evidence of adverse events after cystectomy or brachytherapy. Acute toxicity (<3 months) after cystectomy was seen in 34 patients (52%), including sepsis, UTI, and wound problems. Late toxicity was seen in 30 patients (46%) after cystectomy, including stoma problems and ureter/ureter anastomosis problems. In the brachytherapy group, acute toxicity was observed in 13 patients (17%), with six patients developing wound infections. Eight cases of late toxicity were observed, including five cases of fistula requiring a temporary suprapubic catheter.

In one observational study 19% (57/302) of patients received subsequent salvage cystectomy after primary radical radiotherapy. Similarly, in three trimodality therapy series bladder preservation rates in long-term survivors ranged from 80% to 83%.

Quality of life was reported by one observational study of 58 patients after radical radiotherapy and 251 patients after radical cystectomy. Distress from bowel function was reported in 24% of

cystectomy patients and 32% of radiotherapy patients (RR 0.74, 95% CI 0.45 to 1.21). Factors related to sexual dysfunction were lower after radiotherapy than after cystectomy.

Table 102. GRADE evidence profile: Radical cystectomy versus radical radiotherapy (randomised trials)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	Radiotherapy	Relative (95% CI)	Absolute	
Overall survival at 3 yrs: intent-to-treat analysis											
3[1]	randomised trials	none	none	serious[2]	serious[3]	none	97/221 (43.9%)	63/218 (28.9%)	OR 1.93 (1.3 to 2.87)	151 more per 1000 (from 57 more to 249 more)	⊕⊕OO LOW
Overall survival at 5 yrs: intent-to-treat analysis											
3[1]	randomised trials	none	none	serious[2]	serious[3]	none	74/221 (33.5%)	46/218 (21.1%)	OR 1.87 (1.22 to 2.87)	122 more per 1000 (from 35 more to 223 more)	⊕⊕OO LOW
Overall survival at 3 yrs: treatment received analysis											
2[1]	randomised trials	none	none	serious[2]	serious[3]	none	67/143 (46.9%)	56/173 (32.4%)	OR 1.86 (1.17 to 2.94)	147 more per 1000 (from 35 more to 261 more)	⊕⊕OO LOW
Overall survival at 5 yrs: treatment received analysis											
3[1]	randomised trials	none	none	serious[2]	serious[3]	none	66/173 (38.2%)	45/205 (22%)	OR 2.17 (1.39 to 3.41)	159 more per 1000 (from 62 more to 270 more)	⊕⊕OO LOW
Disease-specific survival at 3 yrs: intent-to-treat analysis											
1[1]	randomised trials	none	none	serious[2]	serious[3,4]	none	44/98 (44.9%)	30/91 (33%)	OR 1.66 (0.92 to 2.99)	120 more per 1000 (from 18 fewer to 266 more)	⊕⊕OO LOW
Disease-specific survival at 5 yrs: intent-to-treat analysis											
1[2]	randomised trials	none	none	serious[2]	serious[3,4]	none	35/98 (35.7%)	26/91 (28.6%)	OR 1.39 (0.75 to 2.57)	72 more per 1000 (from 55 fewer to 221 more)	⊕⊕OO LOW
Disease-specific survival at 10 yrs: intent-to-treat analysis											
1[1]	randomised trials	none	none	serious[2]	serious[3,4]	none	30/98 (30.6%)	18/91 (19.8%)	OR 1.79 (0.91 to 3.5)	108 more per 1000 (from 15 fewer to 265 more)	⊕⊕OO LOW
Disease-specific survival at 3yrs: treatment received analysis											
1[1]	randomised trials	none	none	serious[2]	serious[3]	none	41/77 (53.2%)	31/85 (36.5%)	OR 1.98 (1.06 to 3.72)	167 more per 1000 (from 14 more to 316 more)	⊕⊕OO LOW
Disease-specific survival at 5 yrs: treatment received analysis											
1[1]	randomised trials	none	none	serious[2]	serious[3,4]	none	34/77 (44.2%)	26/85 (30.6%)	OR 1.79 (0.94 to 3.42)	135 more per 1000 (from 13 fewer to 295 more)	⊕⊕OO LOW
Complication rate											
1[1]	randomised trials	none	none	serious[2]	serious[3]	none	60/125 (48%)	75/533 (14.1%)	-	-	⊕⊕OO LOW
Late rectal complications											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	Radiotherapy	Relative (95% CI)	Absolute	
1	randomised trials	none	none	serious[2]	serious[3,5]	none	36%	30%	-	-	⊕⊕OO LOW
Health-related quality of life											
0	No evidence available										
Subsequent treatment											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										

[1] Data from systematic review by Shelley (2001)

[2] No randomised trials comparing surgery alone with radiotherapy alone. 3 trials compared preoperative RT followed by cystectomy versus radical RT with salvage cystectomy. Treatment may not be relevant to current practice.

[3] Low number of events limits precision

[4] Confidence interval includes null value

[5] Number of events and patients not reported

Table 103. GRADE evidence profile: Radical cystectomy versus radical radiotherapy (comparative observational studies)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cystectomy	Radiotherapy	Relative (95% CI)	Absolute	
Overall mortality rate (follow-up median 36-42 months)											
2[1]	observational studies	None	none	none	serious[2]	none	42/103 (40.8%)	39/132 (29.5%)	RR 1.42 (1 to 2.02)	124 more per 1000 (from 0 more to 301 more)	⊕OOO VERY LOW
Overall survival at 3 yrs (follow-up mean 34 months)											
1[3]	observational studies	none	none	none	serious[2]	none	69%	39%	-	Favours surgery (p=0.03)	⊕OOO VERY LOW
Overall survival at 5 yrs											
6[4]	observational studies	none	serious[5]	none	none	none	Range 37% - 53%	Range 21% - 68%	-	5/6 studies showed no difference between treatments	⊕OOO VERY LOW
Overall survival (median OS in patients aged <60 yrs)											
1[6]	observational studies	none	none	none	none	none	1783	214	HR 1.64 (1.34-1.99)	Median OS 74mo after RC vs. 28mo after RT	⊕⊕OO LOW
Overall survival (median OS in patients aged 60-69 yrs)											
1[6]	observational studies	none	none	none	none	none	2474	401	HR 1.54 (1.34-1.76)	Median OS 49mo after RC vs. 24mo after RT	⊕⊕OO LOW
Overall survival (median OS in patients aged 70-79yrs)											
1[6]	observational studies	none	none	none	none	none	2873	931	HR 1.52 (1.38-1.66)	Median OS 33mo after RC vs. 19mo after RT	⊕⊕OO LOW
Overall survival (median OS in patients aged >79yrs)											
1[6]	observational studies	none	none	none	none	none	904	1227	HR 1.32 (1.19-1.46)	Median OS 18mo after RC vs. 15mo after RT	⊕⊕OO LOW
Progression-free survival at 3yrs											
1[7]	observational studies	none	none	none	serious[2]	none	72.5%	69%	-	Uncertainty of a difference between treatments	⊕OOO VERY LOW
Disease-specific survival at 5 yrs											
5[8]	observational studies	none	serious[5]	none	none	none	Range 53%-67%	Range 48%-75%	-	None of the studies reported a significant difference	⊕OOO VERY LOW
Disease-specific survival (median DSS in patients aged<60yrs)											
1[6]	observational studies	none	none	none	none	none	1783	214	HR 1.69 (1.35-2.11)	Median DSS not reached after RC vs. 43mo after RT	⊕⊕OO LOW
Disease-specific survival (median DSS in patients aged 60-69 yrs)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cystectomy	Radiotherapy	Relative (95% CI)	Absolute	
1[6]	observational studies	none	none	none	none	none	2474	401	HR 1.55 (1.32-1.83)	Median DSS 141mo after RC vs. 42mo after RT	⊕⊕OO LOW
Disease-specific survival (median DSS in patients aged 70-79 yrs)											
1[6]	observational studies	none	none	none	none	none	2873	931	HR 1.31 (1.16-1.48)	Median DSS 132mo after RC vs. 40mo after RT	⊕⊕OO LOW
Disease-specific survival (median DSS in patients aged >79 yrs)											
1[6]	observational studies	none	none	none	none	none	904	1227	HR 1.21 (1.07-1.38)	Median DSS 37mo after RC vs. 22mo after RT	⊕⊕OO LOW
Distant recurrence rate (follow-up median 82 months)											
1[9]	observational studies	none	none	none	serious[2]	none	27/72 (37.5%)	33/97 (34%)	RR 1.10 (0.73 to 1.66)	34 more per 1000 (from 92 fewer to 225 more)	⊕OOO VERY LOW
5 yr distant recurrence rate – subgroup cT2 only (follow-up median 46 months)											
1[10]	observational studies	none	none	none	serious[2]	none	9%	12%	-	Uncertainty of a difference between treatments (p=0.4)	⊕OOO VERY LOW
5 yr distant recurrence rate – subgroup cT3 only (follow-up median 46 months)											
1[10]	observational studies	none	none	none	serious[2]	none	62%	31%	-	Favours LCRT but non-significant (p=0.09)	⊕OOO VERY LOW
Treatment-related morbidity: acute toxicity											
1[11]	observational studies	none	none	none	serious[2]	none	34/65 (52.3%)	13/75 (17.3%)	RR 3.02 (1.75 to 5.21)	350 more per 1000 (from 130 more to 730 more)	⊕OOO VERY LOW
Treatment-related morbidity: Late toxicity											
1[11]	observational studies	none	none	none	serious[2]	none	30/65 (46.2%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality (assessed with: 3-month mortality rate)											
1[12]	observational studies	none	none	none	serious[2]	none	8/96 (8.3%)	5/302 (1.7%)	RR 5.03 (1.69 to 15.02)	67 more per 1000 (from 11 more to 232 more)	⊕OOO VERY LOW
Health-related quality of life (assessed with: Distress from bowel function)											
1[13]	observational studies	none	none	none	serious[2]	none	39/166 (23.5%)	15/47 (31.9%)	RR 0.74 (0.45 to 1.21)	83 fewer per 1000 (from 176 fewer to 67 more)	⊕OOO VERY LOW
Health-related quality of life (assessed with: Dissatisfaction with sexual function (males only))											
1[13]	observational studies	none	none	none	serious[2]	none	67%	36%	RR 0.6 (0.4 to 1.0)	Favours RT	⊕OOO VERY LOW
Health-related quality of life (assessed with: Erectile dysfunction)											
1[13]	observational studies	none	none	none	serious[2]	none	92%	75%	HR 0.8 (0.6 to 1.0)	Favours RT	⊕OOO VERY LOW
Subsequent treatment (assessed with: salvage cystectomy in RT group)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cystectomy	Radiotherapy	Relative (95% CI)	Absolute	
1[12]	observational studies	none	none	none	serious[2]	none	-	57/302 (18.9%)	-	-	⊕OOO VERY LOW

[1] Koga (2008): Low-dose chemo-radiation followed by partial or radical cystectomy versus immediate cystectomy; Haresh (2007): Chemo-radiation versus radical cystectomy
[2] Low number of events limits precision
[3] Kalogeras (2008)
[4] Chahal 2003/Munro 2010; Gore 2010; Bekelman 2012; Kotwal 2008; van der Steen-Banasik; Koga 2008
[5] Treatment regimes and length of follow-up varied across studies. Number of events not reported.
[6] Chamie 2008
[7] Mayans (2010): Chemoradiation versus radical cystectomy
[8] Gore 2010; Bekelman 2012; Kotwal 2008; van der Steen-Banasik 2009; Koga 2008
[9] Kotwal 2008: Cystectomy vs radical radiotherapy (no concurrent chemo)
[10] Koga 2008
[11] van der Steen-Banasik 2009
[12] Chahal 2003
[13] Henningsohn 2002

Table 104. GRADE evidence profile: Trimodality therapy (non-comparative series)

Quality assessment							No of patients	Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trimodality therapy	Relative (95% CI)	Absolute	
Overall survival at 5 years										
4[1]	observational studies	None	none	none	none	none	N=1194 Range 51%-68%	n/a	n/a	⊕⊕OO LOW
5-year overall survival with bladder preservation										
3[2]	observational studies	none	none	none	none	none	N=726 Range 80%-83%	n/a	n/a	⊕⊕OO LOW
Local recurrence rate										
3[2]	observational studies	none	none	none	none	none	N=726 Range 34%-40%	n/a	n/a	⊕⊕OO LOW

[1] Mak 2012; Shipley 2002; Rodel 2002; Perdona 2008

[2] Shipley 2002; Rodel 2002; Perdona 2008

Table 105. GRADE evidence profile: Radical cystectomy (non-comparative series)

Quality assessment							No of patients	Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radical cystectomy	Relative (95% CI)	Absolute	
Overall survival at 5 years										
1[1]	observational studies	none	none	none	none	none	N=1100 58%	n/a	n/a	⊕⊕OO LOW
Recurrence-free survival at 5 years										
2[2]	observational studies	none	none	none	none	none	N=4108 70%	n/a	n/a	⊕⊕OO LOW
Disease-specific survival at 5 years										
3[3]	observational studies	none	none	none	none	none	N=6591 Range 65%-76%	n/a	n/a	⊕⊕OO LOW

[1] Hautmann 2012

[2] Rink 2012; Hautmann 2012

[3] Rink 2012; Hautmann 2012; Otto 2012

Table 106. 5-yr survival rates in comparative studies of radical cystectomy versus radical radiotherapy

Study, n patients	Treatment	5-yr survival Cystectomy	5-yr survival Radiotherapy	Salvage RC	Prognostic factors
Chahal 2003/ Munro 2010 N=383 (302 RT, 96 RC)	RC versus RT (55Gy in 20 fractions over 28/30 days)	OS=37% 10-yr OS =24%	OS=37% 10-yr OS =22%	19%, median 14.8mo after RT	T-stage, hydronephrosis, surgery vs. RT for those who survive 2yr post-op (HR 0.66, 95% CI 0.44-1.01)
Gore 2010 N=1600 (678 RC, 922 bladder sparing)	RC (includes in combination with RT or CT) versus bladder sparing approaches (CT/RT or combination)	OS = 42% DSS = 67%	OS = 21%* DSS = 48%		
Bekelman 2012 N=1843 (1426 RC, 417 cisplatin-based bladder sparing)	No details – abstract only	OS = 47% DSS=65%	OS = 28%† DSS = 52%		
Kotwal 2008 N=169 (72 RC, 97 EBRT)	RC versus EBRT (50-55Gy in 20 fractions over 4 weeks, no concurrent chemo)	OS= 41% DSS= 53%	OS= 35% DSS=57%		Hydronephrosis and grade
Steen-Banasik 2009 N=141 cT2 only (65 RC, 75 BT)	RC versus brachytherapy (EBRT and BT)	OS = 52% DSS = 60%	OS=57% DSS= 71%	69% preserved bladder	Age
Koga 2008 N=192 (73 RC, 119 chemorad + RC or PC)	RC versus CTRT (40Gy in 4 wks with 2 cycles of Cisplatin 20mg/day for 5 days, based on tumour status at 4-6wks patients had RC or PC)	OS = 53% DSS = 61%	OS= 68% DSS=75%		Stage cT3 CTRT group had better OS (53% v 22%) and DSS (62% v 27%) than RC group.

*significant difference between treatment groups in favour of cystectomy
†unadjusted 5-yr survival % - differences in DSS and OS between treatment groups were non-significant after adjusted instrumental variable analysis

Table 107. Results of trimodality therapy in bladder preservation series

	Mak 2012 (RTOG studies)	Shipley (2002)	Rodel (2002)	Perdona (2008)
Treatment	Varying protocols	Varying protocols	Varying protocols	Varying protocol
Number pts	468	190	415	121
Median follow-up (mo)	51	80	60	66
Complete response rate	72%	64%	72%	86%
5-yr overall survival	57%	54%	51%	68%
10-yr overall survival	36%	36%	31%	
5-yr overall survival with bladder preservation		45%	42%	51%
Bladder preservation in long-term survivors		83%	82%	80%
Local recurrence rate		40%	35%	34%
Distant mets rate	31% (5-yr)			33% (5-yr for complete response patients); 47% (5-yr with residual tumour)

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Rink, M et al. Does increasing the nodal yield improve outcomes in patients without nodal metastasis at radical cystectomy? World Journal of Urology 2012; 30(6): 807-814.

Rodel, C et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. Journal of Clinical Oncology 2002; 20(14): 3061-3071.

Shelley, M et al. Surgery versus radiotherapy for muscle invasive bladder cancer. Cochrane Database of Systematic Reviews 2001, Issue 4. Art. No.: CD002079. DOI: 10.1002/14651858.CD002079

Shipley, WU et al. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urology 2002; 60(1): 62-67.

Steen, BE et al. Brachytherapy versus cystectomy in solitary bladder cancer: a case control, multicentre, East-Netherlands study. Radiotherapy.& Oncology 2009; 93(2): 352-357.

References to excluded studies (with reasons for exclusion)

Cervek, J et al. Invasive bladder cancer: our experience with bladder sparing approach. International Journal of Radiation Oncology, Biology, Physics 1998; 41(2): 273-278.

Reason: Not relevant to PICO – primary chemotherapy

Graham, JD et al. Palliative radiotherapy for muscle invasive bladder cancer: final results of a prospective randomised trial of two radiotherapy schedules. British.journal of cancer 2000; 83(Suppl 1): 27

Reason: Not relevant to PICO – palliative radiotherapy

Kaufman, DS et al. The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. The Oncologist 2000; 5(6): 471-476.

Reason: Non-comparative – included in pooled analysis by Mak (2012)

Shipley, WU et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. Journal of

clinical.oncology : official.journal of the.American.Society.of Clinical.Oncology 1998; 16(11): 3576-3583.

Reason: Included in pooled analysis by Mak (2012)

McBain, CA et al. Radiotherapy for muscle invasive carcinoma of the bladder: results of a randomised trial comparing conventional whole bladder with dose-escalated partial bladder radiotherapy [abstract]. International.Journal of Radiation.Oncology Biology.Physics. 2002; 54(2 Suppl): 61-62.

Reason: Not relevant to PICO

Cowan, RA et al. Radiotherapy for muscle-invasive carcinoma of the bladder: results of a randomized trial comparing conventional whole bladder with dose-escalated partial bladder radiotherapy. International.journal of radiation.oncology, biology., physics. 2004; 59(1): 197-207.

Reason: Not relevant to PICO

Clark, PE et al. Radical cystectomy in the elderly: comparison of clincal outcomes between younger and older patients. Cancer 2005; 104(1): 36-43.

Reason: Comparison not relevant to PICO – no RT

Nieuwenhuijzen, JA et al. Survival after bladder-preservation with brachytherapy versus radical cystectomy; a single institution experience. European Urology 2005; 48(2): 239-245.

Reason: Population not relevant to PICO – 50% T1, not reported separately

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Reason: Non-comparative (n=24)

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Reason: Expert review

Huddart, R. Updated results of the BC2001 phase III randomized trial of standard vs reduced high dose volume radiotherapy for muscle invasive bladder cancer (ISCRTN:68324339): Tumour control, toxicity and quality of life. European Journal of Cancer, Supplement 2009; Conference(var.pagings): 2-3.

Reason: Not relevant to PICO

Huddart, RA et al. A multicenter phase III randomized trial of standard versus reduced volume radiotherapy for muscle invasive bladder cancer (ISCRTN:68324339) [abstract no. 5022]. Journal of Clinical.Oncology 2009; 27(15S Part I): 240

Reason: Not relevant to PICO

James, ND. Results of a phase III randomized trial of synchronous chemoradiotherapy (CRT) compared to radiotherapy (RT) alone in muscle-invasive bladder cancer (MIBC) (BC2001 CRUK/01/004). Journal of Clinical Oncology 2010; Conference(var.pagings): 15

Reason: Not relevant to PICO

James, ND et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. The.New England.journal of medicine 2012; 366(16): 1477-1488.

Reason: Not relevant to PICO

Orsatti, M. Organ preservation by the association of chemotherapy and radiotherapy in invasive bladder cancer. Current Drug Therapy 2010; 5(3): 202-210.

Reason: Expert review

Barbiere, JM et al. Trends in the use of radiotherapy and radical surgery for patients with bladder urothelial cell carcinoma in East Anglia, 1995-2006. BJU International 2011; 108(7): 1106-1114.

Reason: No clinical outcomes

Li, K et al. Systematic review and meta-analysis of comparative studies reporting early outcomes after robot-assisted radical cystectomy versus open radical cystectomy. Cancer Treatment Reviews 2013; 39(6): 551-560.

Reason: Not relevant to PICO

Solsona, E et al. Bladder preservation in selected patients with muscle-invasive bladder cancer by complete transurethral resection of the bladder plus systemic chemotherapy: long-term follow-up of a phase 2 nonrandomized comparative trial with radical cystectomy. European.Urology 2009; 55(4): 911-919.

Reason: Comparison not relevant to PICO (RC v Chemo)

Rathore, PS. A 5-year retrospective review of a non-randomized cohort of 123 patients undergoing radical radiotherapy or radical cystectomy in Newcastle, NSW, Australia. BJU International 2013; Conference(var.pagings): 72

Reason: Abstract only – insufficient information for inclusion

Shih, C and Porter, MP. Health-related quality of life after cystectomy and urinary diversion for bladder cancer. Advances in Urology 2011; 2011: 715892

Reason: Narrative review

Porter, MP and Penson, DF. Health related quality of life after radical cystectomy and urinary diversion for bladder cancer: a systematic review and critical analysis of the literature. [Review] [20 refs]. Journal of Urology 2005; 173(4): 1318-1322.

Reason: Not relevant to PICO

Tekin, A, Aki, FT, and Ozen, H. Radical cystectomy versus alternative treatments for muscle-confined bladder cancer. International Urology & Nephrology 2001; 33(2): 357-362.

Reason: Not relevant to PICO (RT group includes patients who had no treatment)

Ramani, VA et al. Differential complication rates following radical cystectomy in the irradiated and nonirradiated pelvis. European Urology 2010; 57(6): 1058-1063.

Reason: Not relevant to PICO (includes non bladder primaries)

Eswara, JR et al. Complications and long-term results of salvage cystectomy after failed bladder sparing therapy for muscle invasive bladder cancer. Journal of Urology 2012; 187(2): 463-468.

Reason: Not relevant to PICO (salvage cystectomy)

Szymanski, KM et al. External stoma and peristomal complications following radical cystectomy and ileal conduit diversion: a systematic review. [Review]. Ostomy Wound Management 2010; 56(1): 28-35.

Reason: Relevant to another topic

Maarouf, AM et al. Bladder preservation multimodality therapy as an alternative to radical cystectomy for treatment of muscle invasive bladder cancer. BJU International 2011; 107(10): 1605-1610.

Reason: Not relevant to practice (Egypt)

Mameghan, H et al. The management of invasive transitional cell carcinoma of the bladder. Results of definitive and preoperative radiation therapy in 390 patients treated at the Prince of Wales Hospital, Sydney, Australia. Cancer 1992; 69(11): 2771-2778.

Reason: Not relevant to current practice

Canobbio, L et al. A randomized study between neo-adjuvant chemo-radiotherapy (CT-RT) before radical cystectomy and cystectory alone in bladder cancer. Annals.of Oncology 1994; 5(Suppl 8): 62

Reason: Not relevant to current practice

Cole, CJ et al. Local control of muscle-invasive bladder cancer: preoperative radiotherapy and cystectomy versus cystectomy alone. International Journal of Radiation Oncology, Biology, Physics 1995; 32(2): 331-340.

Reason: Not relevant to current practice

Smith, JA, Jr. et al. Treatment of advanced bladder cancer with combined preoperative irradiation and radical cystectomy versus radical cystectomy alone: a phase III intergroup study. Journal of Urology 1997; 157(3): 805-807.

Reason: Not relevant to current practice

Azuma, H et al. Total cystectomy versus bladder preservation therapy for locally invasive bladder cancer: effect of combined therapy using balloon-occluded arterial infusion of anticancer agent and hemodialysis with concurrent radiation. American Journal of Clinical Oncology 2009; 32(6): 592-606.

Reason: Not relevant to current practice

Granfors, T, Tomic, R, and Ljungberg, B. Downstaging and survival benefits of neoadjuvant radiotherapy before cystectomy for patients with invasive bladder carcinoma. Scandinavian Journal of Urology & Nephrology 2009; 43(4): 293-299.

Reason: Not relevant to current practice

Zapatero, A et al. Long-term results of two prospective bladder-sparing trimodality approaches for invasive bladder cancer: neoadjuvant chemotherapy and concurrent radio-chemotherapy. Urology 2012; 80(5): 1056-1062.

Reason: <100 patients in trimodality therapy series

Somani, BK et al. Quality of life and body image for bladder cancer patients undergoing radical cystectomy and urinary diversion--a prospective cohort study with a systematic review of literature. Urology 2009; 74(5): 1138-1143.

Reason: Relevant to another topic

Takada, N et al. Peri-operative morbidity and mortality related to radical cystectomy: a multi-institutional retrospective study in Japan. BJU International 2012; 110(11 Pt B): E756-E764.

Reason: Non-comparative

Rene, NJ. Conservative treatment of invasive bladder cancer. Current Oncology 2009; 16(4): 36-47.

Reason: Expert review

Sapre, N, Anderson, P, and Foroudi, F. Management of local recurrences in the irradiated bladder: a systematic review. BJU International 2012; 110 Suppl 4: 51-57.

Reason: Not relevant to PICO

Aluwini, S et al. Bladder Function Preservation With Brachytherapy, External Beam Radiation Therapy, and Limited Surger in Bladder Cancer Patients: Long-Term Results. International Journal of Radiation Oncology Biology Physics 2014; 88(3): 611-617.

Reason: Not relevant to PICO

Evidence tables

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Chahal 2003/ Munro 2010

UK</td>
<td>Retrospective review

1993-1996</td>
<td>N=398 (302 RT, 96 RC)</td>
<td>
<table>
<tr><th></th><th>RT N (%)</th><th>RC N (%)</th></tr>
<tr><td>Mean age*</td><td>71</td><td>66</td></tr>
<tr><td>Female</td><td>106 (35)</td><td>32 (33)</td></tr>
<tr><td>Male</td><td>196 (65)</td><td>64 (67)</td></tr>
<tr><td>Diabetes</td><td>25 (8)</td><td>7 (7)</td></tr>
<tr><td>Cardiac disease*</td><td>120 (40)</td><td>23 (24)</td></tr>
<tr><td>Neurologic disease*</td><td>24 (8)</td><td>2 (2)</td></tr>
<tr><td>ASA Grade 1</td><td>84 (28)</td><td>32 (33)</td></tr>
<tr><td>ASA Grade 2</td><td>162 (49)</td><td>44 (46)</td></tr>
<tr><td>ASA Grade 3</td><td>68 (22)</td><td>20 (21)</td></tr>
<tr><td colspan="3">Clinical stage/grade</td></tr>
<tr><td>TxGx</td><td>2 (<1)</td><td>1 (<1)</td></tr>
<tr><td>T1G3</td><td>9 (3)</td><td>4 (4)</td></tr>
<tr><td>T2</td><td>156 (52)</td><td>42 (44)</td></tr>
<tr><td>T3</td><td>116 (38)</td><td>33 (34)</td></tr>
<tr><td>T4</td><td>19 (6)</td><td>16 (17)</td></tr>
</table>
ASA, American Society of Anaesthesiologists
*p<0.5
</td>
<td>96 had surgery – 88 RC with ileal conduit diversion, 8 (8.3%) had continent urinary diversion. Pelvic lymphadenectomy performed in majority. Urethrectomy in 18 (16.6%) of male patients. Bowel preparation, antibiotics and thromboembolic prophylaxis used in all patients.</td>
<td>302 radical radiotherapy – 55 Gray in 20 fractions over 28 or 30 days (>90% received this regimen). Planning CT in all cases and RT given by 3-field technique with an empty bladder. Recurrence treated endoscopically or with RC.

57/302 (18.8%) salvage RC, median 14.8mo (range 4.6-52mo) after RT, mostly with ileal conduit diversion.

43.6% had recurrence in bladder (17% Ta, 10% CIS, 15% T1, 40% ≥T2). In 18%</td>
<td>5 yr survival (Chahal 2033) and 10 yr survival (Munro 2010)</td>
<td>Treatment-related morbidity: Cystectomy: Peri-operative complications (before hospital discharge)
RC – Gastrointestinal 12/96 (12%), salvage RC 10/57 (17.5%). Cardiac 9/96 (6%), salvage RC 2/57 (3.5%)

Short-term complications (within 3mo of discharge)
RC – intestinal obstruction 6 (6%), salvage 1 (1.7%). Urosepsis 7 (7%), salvage nil. Renal failure (salvage only) 4 (7%).
Long-term complications:
RC – renal failure 3 (3%), slavage nil. Intestinal obstruction 3 (3%), salvage 2 (3.5%). Hernia 5 (5%), salvage nil

Radiotherapy: moderate-severe urinary complications</td>
<td></td>
<td>Unable to report cancer-specific deaths – RT patients were older and had more cardiac and other co-morbidities. RC patients more likely to have clinical stage T4 and high grade. No neoadjuvant CT or extended lymphadenectomy.</td>
</tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
					of cases the recurrence was fulgurated (presumed superficial)		39/302 (13%). Severe complications with bladder incapable of functioning normally or requiring surgical intervention 18 (5.2%). Significant GI complications 20 (6.6%). Minor diarrhoea 48 (15.9%). Mild-mod frequency 47 (15.5%) **Treatment-related mortality** 3-mo mortality for RC=8.3% (8/96), for salvage cystectomy = 15.7% (9/57), for RT = 1.65% (5/302) **Survival** Kaplan Meier curves. 5-yr OS for RT 37.4% vs. 36.5% RC (ns) Gender, ASA and T-stage were independent predictors of 5-yr survival in multivariate analyses. 10-yr survival 21.6% RT vs. 24.1% RC (ns) Multivariate analyses suggest a 34% survival advantage for surgery vs. RT for those who survive 2y post-operatively (HR 0.66,		

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>0.44-1.01). T stage and presence of hydronephrosis are associated with 10-y survival.</td><td></td><td></td></tr>
<tr><td>Kozak 2012

USA</td><td>Retrospective review of SEER database

1988-2006</td><td>N=26,851

Included >20y old, first malignancy, TCC, SCC or AC, counties with at least 25 cases, non-metastatic muscle invasive disease</td><td><table><tr><th></th><th>No T %</th><th>RT %</th><th>RC %</th></tr><tr><td>Age</td><td></td><td></td><td></td></tr><tr><td>21-50</td><td>3.2</td><td>4.0</td><td>92.8</td></tr><tr><td>51-70</td><td>2.4</td><td>6.6</td><td>91.0</td></tr><tr><td>71-80</td><td>2.6</td><td>12</td><td>85.4</td></tr><tr><td>>80</td><td>3.8</td><td>18.5</td><td>77.7</td></tr><tr><td></td><td></td><td></td><td></td></tr><tr><td>Male</td><td>2.6</td><td>10.5</td><td>86.9</td></tr><tr><td>Female</td><td>3.5</td><td>12</td><td>84.5</td></tr><tr><td></td><td></td><td></td><td></td></tr><tr><td>G1</td><td>7.3</td><td>2.4</td><td>90.4</td></tr><tr><td>G2</td><td>3.5</td><td>5.4</td><td>91</td></tr><tr><td>G3</td><td>2.5</td><td>11.3</td><td>86.2</td></tr></table>
RT patients tended to be older, female, SCC or poorly differentiated tumours,</td><td>Definitive surgery n=23,162 (surgical resection alone or cystectomy plus RT)</td><td>No definitive treatment n=757 (no surgery or EBRT)

Definitive RT n=2932 (EBRT with or without TURBT)</td><td></td><td>Overall survival
Kaplan-Meier: Median survival = 14mo no treatment, 17mo definitive RT, 43mo definitive surgery (p<0.001)
Multivariate analyses accounting for patient and tumour characteristics found no survival detriment to the utilization of RT compared to surgery (HR 1.002, 95% CI 0.999-1.005). controlling for age, gender, treatment, race, grade, histology and yr of diagnosis.</td><td></td><td>Tumour stage not included in multivariate model. Use of chemo not reported.</td></tr>
<tr><td>Gore 2010

USA</td><td>Retrospective review SEER database

1992-2002</td><td>N=3262, 66 yrs or older with stage II MIBC and no mets.

1162 (51%) were deemed to have no aggressive treatment and were categorised</td><td><table><tr><th></th><th>RC, n(%)</th><th>RT/CT, n(%)</th></tr><tr><td>Mean age</td><td>74.5y</td><td>78.8y</td></tr><tr><td>Male</td><td>480 (71)</td><td>656 (71)</td></tr><tr><td>Female</td><td>198 (29)</td><td>266 (29)</td></tr><tr><td colspan="3">Charlston comorbidity index</td></tr><tr><td>0</td><td>526 (78)</td><td>575 (62)</td></tr><tr><td>1</td><td>102 (15)</td><td>218 (24)</td></tr><tr><td>2</td><td>33 (5)</td><td>80 (9)</td></tr><tr><td>≥3</td><td>17 (2)</td><td>49 (5)</td></tr><tr><td></td><td></td><td></td></tr><tr><td>High</td><td>601 (89)</td><td>825 (90)</td></tr></table></td><td>Radical cystectomy (n=678, 21%) – includes surgery in combination with RT or CT</td><td>Bladder sparing approaches – includes CT alone (n=402), RT alone (n=271), combination treatment (n=249)</td><td>Mean = 39mo for RC patients, 20.3mo for CT/RT patients, 12.1mo for surveillance group</td><td>Overall survival: CT/RT versus RC (HR of death = 1.5, 95% CI 1.3-1.8).
5-yr adjusted survival = 42.2% (95% CI 39.1-45.4%) for RC; 20.7% (18.7-22.8%) for RT/CT
No statistically significant interaction between age or gender and treatment group.
Disease-specific</td><td>No conflicts of interest declared</td><td>Instrumental variable methods used as substitute for randomisation which balances treatment groups for measured and unmeasured confounders</td></tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
		into surveillance group	grade Patients who underwent cystectomy were younger, had fewer comorbid conditions and were more likely to have high grade cancer.				**survival:** CT/RT versus RC (HR of death = 1.37, 95% CI 1.01-1.77). 5-yr adjusted DSS = 66.6% (95% CI 62.9-70.3%) for RC; 48% (44.5-51.9%) for RT/CT (Adjusted for measured and unmeasured differences between treatment groups)		
Bekelman 2012 USA	Retrospective review SEER database 1995-2005	N=1843, aged >65 yrs, diagnosed with stage II/III UCB	Patients who received BPT were older and more likely to have comorbid disease.	Radical cystectomy (n=1426)	Bladder preservation therapy (BPT) (cisplatin-based) (n=417)	NR	**Disease-specific survival:** unadjusted 5-yr DSS = 64.5% in RC versus 52.2% in BPT **Overall survival:** unadjusted 5-yr OS = 46.5% RC group versus 27.9% BPT group. Using local care cystectomy rate (proportion of all other patients in an individual's regional health care market who received RC) as an instrument, IVM demonstrated no differences in survival (HR for death any cause = 1.06, 95% CI 0.78-1.31), or DSS (HR death bladder cancer=0.94, 95% CI 0.55-1.18)		Abstract only. Instrumental variable methods (IVM) used to address unmeasured confounding.
Kotwal 2008	Retrospective review	N=169 Salvage RC at	RC / RT Median 68.2y / 75.3y	Cystectomy (n=89 – 72 as primary	Radical radiotherapy	Median = 82.8mo RC	**Overall survival:** 45/72 RC died, 69/97 RT died.		

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
UK	1996-2000	recurrence after RT not included	<table><tr><td>age</td><td></td><td></td></tr><tr><td>Age range</td><td>37-85</td><td>43-99</td></tr><tr><td>male</td><td>47 (65%)</td><td>73 (75%)</td></tr><tr><td>Female</td><td>25 (35%)</td><td>24 (25%)</td></tr><tr><td colspan="3">Pre-op clinical stage</td></tr><tr><td>T3 or higher</td><td>46.2%</td><td>51.1%</td></tr><tr><td>Grade 3</td><td>86.4%</td><td>85.3%</td></tr><tr><td>Hydrone-phrosis</td><td>45.6%</td><td>13.3%</td></tr><tr><td>Previous treatment for NMIBC</td><td>25%</td><td>25%</td></tr></table>	radical treatment) 68/72 had RC with ileal conduit formation, 2 patients had continent diversion, 2 had partial cystectomy 52 had standard pelvic lymphadenectomy, 2 iliac sampling, 17 no formal lymph node dissection. 17% men had urethrectomy. 4 patients had adjuvant chemo, 1 neoadjuvant chemo 18 patients downstaged and 16 upstaged at RC	(EBRT) (n=97) 50-55Gy of mega-voltage photons using a linear accelerator in 20 fractions over 4-wks. 1 patient received 57.2Gy in 21 fractions over 5 wks. All had planning CT. No concurrent chemo/radiation, 1 neoadjuvant chemo At 1st follow-up check 16 .5% had superficial recurrence, 7.2% had persistent MIBC, 4 had salvage surgery. A further 5 subsequently required salvage surgery for recurrence	group and 68.1mo RT group	Kaplan-Meier 5yr OS=41.3% RC vs. 34.6% RT (ns) **Disease-specific survival:** 32/72 RC, 37/97 RT died from bladder cancer. 5-yr DSS = 53.4% RC vs. 56.8% RT. 8-yr DSS = 53.4% RC vs. 54.9% RT (ns) **Distant recurrence-free survival** 27/72 RC group vs. 33/97 RT group had regional or distant recurrence. No difference in Kaplan-Meier distant recurrence (p=0.507). **Death within 1-yr of treatment** 25/72 (34.7%) RC vs 21/97 (21.6%) RT Hydronephrosis and grade showed independently significant associations with 3 measures of survival. Treatment did not show an association with OS, DSS or DFRS. More recent RT cohort using 3 or 4 field 3D conformal technique using multileaf		

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							collimators (n=76) the 2-yr DSS was 75.5%		
Van der Steen-Banasik 2009 Netherlands	Retrospective case-control 1991-2001 cystectomy 1983-2002 brachytherapy	141 T1G3 or T2N0M0 Solitary tumours, <5cm	<table><tr><th></th><th>RC (n=65)</th><th>BT (n=75)</th></tr><tr><td>Mean age</td><td>63.3</td><td>68.3</td></tr><tr><td>M / F</td><td>52/13</td><td>67/9</td></tr><tr><td>Multiplicity</td><td>0/65</td><td>9/67</td></tr><tr><td>cT1/cT2</td><td>0/65</td><td>15/61</td></tr><tr><td>Grade 2/3</td><td>6/53</td><td>13/60</td></tr></table> BT group older, more cT1 and more multiple tumours	RC – 65% RC (n=42) and curtaneous ureteroileostomy, 34% (n=22) orthotopic neobladder, 1 patient Indiana pouch. 53/65 pelvic lymphadenectomy. Median hospitalisation time 21 days (range 8-177)	Brachytherapy – combination TURT, EBRT and interstitial brachytherapy. EBRT 3-4 fractions of 3.5Gy in 1 week in cT1 tumours or 20 fractions of 2 Gy in 4 weeks in cT2 tumours. Irradiation dose prescribed at 0.5cm from axis of source. 60 or 30 Gy dose depending on short or long course. Always low dose over 6 or 3 days. Mean hospitalisation time =10 days.	Median 5.7y for BT group and 5.05y for RC group	T-stage, grade, multiplicity did not affect overall or disease-specific survival. **OS:** Age, HR = 1.06 (1.03-1.08) 6% higher risk of dying per yr of age at start of treatment. HR for treatment type not significant for OS or DSS Kaplan-Meier: **5/10 yr OS** = 57%/33% for BT and 52%/42% for RC. **5/10yr DSS=** 71%/66% for BT and 60%/57% for RC No difference between groups even when adjusted for age. **Recurrence:** 22/65 RC (9 distant mets) 35/76 BT (10 distant mets). 52/75 patients preserved bladder **Morbidity (CTC):** 72% (n=47) RC-related adverse events. Acute toxicity 52% (n=34), late toxicity 46% (n=30). 2 RC-related deaths. Acute toxicity 17% (n=13/75) for BT. Late toxicity11% (8/75).		

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Kalogeras 2008 Greece	Retrospective review 1995-2006	145 T2M0N0 119 RT and 26 RC	<table><tr><th></th><th>RT (n=119)</th><th>RC (n=26)</th></tr><tr><td>>70y</td><td>80</td><td>16</td></tr><tr><td>≤70y</td><td>39</td><td>10</td></tr><tr><td>Grade 2</td><td>13</td><td>6</td></tr><tr><td>Grade 3</td><td>88</td><td>16</td></tr><tr><td>Grade 4</td><td>18</td><td>3</td></tr></table>	RC: 22 (85%) ileal conduit diversion, 4 (15%) orthotopic neobladder pouch	RT: linear accelerator (6MV) using Box technique. Total dose 64 Gy (range 60-66) in 32-36 fractions. 44Gy to pelvis and 20 Gy as boost. Daily dose=1.8-2.0 Gy	Mean 38.4mo RT and 37.2mo RC	**Overall survival:** Kaplan-Meier, 3-yr OS, 69% RC and 39% RT (p=0.032). No difference between >70y and <70y in either treatment group. **Distant-mets:** 14% >70y RT, 20% ≤70y RT, 7.6%>70y RC, 7.4%≤70y RC. **Morbidity: RT:** Grade1/2 nausea vomiting (26%, n=31), G1/2 cystitis 64 (54%,n=64), G1/2 diarrhoea (24%, n=28) Grade 3 events (n=19, 16%). Grade 1 or 2 leukopenia (55%, n=99), G1/2 anemia (44%, n=52), G1/2 thrombocytopenia (18%, n=20) RC complications: acute or late 46% (12/26). 1 death due to pulmonary embolism.		
Haresh 2007 India	Comparative study (appears prospective) 2002-2004	N=43 T2-T2, any N, M0 Allocated to treatment according to patient preference	<table><tr><th></th><th>Surgery n=30</th><th>CTRT n=13</th></tr><tr><td>Male</td><td>29 (97%)</td><td>12 (92%)</td></tr><tr><td>Female</td><td>1 (3%)</td><td>1 (8%)</td></tr><tr><td>Stage II</td><td>10 (33%)</td><td>4 (31%)</td></tr><tr><td>Stage III</td><td>16 (53%)</td><td>4 (31%)</td></tr><tr><td>Stage IV</td><td>4 (13%)</td><td>5 (39%)</td></tr><tr><td>Grade II</td><td>3 (10%)</td><td>4 (31%)</td></tr><tr><td>Grade III</td><td>15 (50%)</td><td>5 (39%)</td></tr></table>	Radical cystectomy: adjuvant chemo given for T3/T4 or node +ve disease only – 4 cycles given 3-weekly starting 2wks after surgery (Cisplatin/ Methotrexate/	Chemo-radiation: 2 cycles neoadjuvant CMV chemotherapy 3wkly followed by concurrent chemoradiation. RT started after		**Metastases:** RC 5/30 (17%). 60% free of disease after 2yrs. CTRT 4/13 (31%). 62% free of disease after 2yrs. **Overall mortality:** 10/30 (33%) died RC arm vs. 4/13 (31%) CTRT arm. 2-yr survival rate 56%		

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			Grade IV: 12 (40%) / 4 (31%)	Vinblastine) 60% ileal conduit diversion, 33% sigmoid neobladder, 1 indiana pouch, 1 ureterostomy	2-3wks depending on blood count. EBRT 60Gy/ 30 fractions /6 wks with concurrent inj cisplatin 40mg/m^2 wkly IV. Initial 40Gy delivered by 4-field box technique to whole pelvis, 20Gy delivered by 3DCRT to the bladder without gap between treatment.		RC vs. 54% CTRT (p=0.93) **Morbidity:** 7/30 (23%) had significant post-operative complications. 4(36%) had significant chemo toxicity (3 grade3/4 neutropenia). No significant Grade 3 /4 side-effects in CTRT arm. 2 patients Grade 1 neutropenia. **Treatment-related mortality:** 4/30 (13%) RC arm - 1 post-op respiratory failure, 1 post op sx complication, 1 adj chemo toxicity, 1 septicaemia.		
Koga 2008 Japan	Retrospective review 1997-2007 CTRT+RC/PC 1983-1997 immediate RC	192 T2-T4aN0M0	LCRT n=119 / RC n=73 Female: 31 (26%) / 13 (18%) male: 88 (74%) / 60 (82%) Median age: 70 / 67 T2: 64 (54%) / 38 (52%) T3: 46 (39%) / 30 (41%) T4a: 9 (8%) / 5 (7%) Clinical: 50 / -	LCRT: after TURBT, total dose 40Gy (200 cGy/day) irradiated to bladder in 4 wks with 2 cycles of CT Cisplatin (20mg/day for 5d) during 1st and 4th wk of R. Based on tumour status at 4-6wks after LCRT patient had RC or PR with curative intent. PC for patients who	Immediate RC: no neoadjuvant therapy. Patients had adjuvant CT if RC specimen showed pathological lymph node mets, pathological T3 or T 4 and/or T2 with vascular invasion. 3 or more cycles of combined	Median 36mo LCRT group, 46mo immediate RC group	**Overall mortality:** 35/119 (29%) LCRT vs. 32/73 (44%) RC group. 5-yr OS 68% LCRT vs. 53% RC, p=0.13 **Disease-specific mortality:** 27/119 (23%) LCRT vs. 26/73 (36%) RC. 5-yr DSS = 75% vs. 61%, p=0.11 In clinical stage T3 the LCRT had better survival than RC group 5-yr OS 53% vs. 22%, p=0.007. 5-yr DSS 62% vs. 27%,		Short follow-up

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			response (42%) Not CR 69 (58%) - Surgery method RC 65 (55%) 100% PC 24 (20%) No 30 (25%) Median LNs removed 8 12 Adj CT - 29 (41%) Patients in the LCRT group were older.	had complete response or almost CR and whose invasive cancers did not originally involve bladder neck or trigone. All had bilateral pelvic lymph node dissection.	cisplatin-based chemo were given every 4 wks.		p=0.006. **Distant recurrence rate:** 5-yr rate for cT2 12% vs. 9% RC, p-0.44. 5-yr rate for cT3 lower for LCRT, 31% vs. 62% RC, p=0.09		
Mayans 2010 Spain	Retrospective review 1994-2007 1997-2003 chemo A regime 2003-2007 chemo B regime	43 chemoradiation 145 radical cystectomy	Patients undergoing trimodal therapy T1 1 (2.3%) T2 19 (44.1%) T3 15 (34.9%) T4 8 (18.6%) G1 0% G2 7 (16.3%) G3 36 (83.7%) Hydronephrosis 28.9% Chemo A 41.7% Chemo B 58.3% RT dose >60Gy 59.3% RT dose <60Gy 40.7% Patients were recommended radical surgery but preferred bladder	Chemo A (n=18): TUR+2 cycles of methotreaztae-5-fluorouracil-cisplatin. RT dose ranging from 45-65Gy with cisplatin-5-fluorouacil. Consolidation with 2 additional chemo cycles. Chemo B (n=25): 2 cycles of gem/cisplatin. Intensity modulated RT (55-65Gy) with Gem/Cis.	Radical cystectomy (n=145)	Median follow-up 39 mo for chemo-rad group and 18mo for RC group.	**Progression-free survival:** 3-yr PFS 69% chemo-rad vs. 72.5% RC 5-yr PFS 58% vs. 63% RC (p=0.83) 2 patients in bladder preservation group had salvage cystectomy. 53.5% had intact bladder and free of disease.	No conflicts of interest	No details of patient characteristics undergoing cystectomy. Short follow-up time.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			sparing approaches. Patients managed with bladder preservation had poorer clinical stage than patients undergoing cystectomy.	Consolidation with 2 additional chemo cycles. RC indicated for patients with partial or no response					
Mak 2012 USA	Pooled analysis of 6 RTOG studies (5 phase II, one phase III)	N=468	The analysis was based on a total of 468 patients with a median age of 66 years; 64% were younger than age 70, 19% were aged 70 to 75, and 17% were older than age 75. Among all patients, 82% were male. Approximately 94% had transitional cell carcinoma; 61% had clinical stage T2 tumours, and 35% had clinical stage T3, 3.9% T4a. 89% had a Zubrod PS of 0.	These small trials all utilized combined-modality therapy with a variety of neoadjuvant and/or adjuvant regimens. Two trials included two cycles of neoadjuvant chemotherapy, one trial had no neoadjuvant or adjuvant chemotherapy, and three incorporated adjuvant chemotherapy.	N/A	Median follow-up was 4.3 years for all patients and 7.8 years among 205 survivors.	72% of patients had a complete response to combined-modality therapy. **Overall survival** 5- and 10-year estimated overall survival rates = 57% and 36%, respectively; **Disease-specific survival** 5- and 10-year estimated disease-specific survival rates = 71% and 65%. The majority of local failures in the bladder were non–muscle invasive, with an estimated 5- and 10-year incidence of 31% and 36%. The 5- and 10-year estimates for muscle-invasive failure rates were 13% and		Abstract only

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>14%, and 5- and 10-year estimates of distant metastases were 31% and 35%.
Multivariate analysis adjusted for age and histology found that higher clinical T stage (cT2vs cT3/4) was associated with decreased overall and disease-specific survival. (10-year DSS: 69% vs. 60%; p = 0.05, 10-year OS: 41% vs. 30%; p = 0.002) Elderly (age ≥ 75) patients did not have significantly different disease-specific survival compared with younger (age 70-75 and age < 70) patients (64% vs 61% vs 67% at 10 years, respectively)
<table>
<tr><th></th><th>5-yr %</th><th>10-y %</th></tr>
<tr><td>OS</td><td>57</td><td>36</td></tr>
<tr><td>DSS</td><td>71</td><td>65</td></tr>
<tr><td>Invasive local failure</td><td>13</td><td>14</td></tr>
<tr><td>Distant mets</td><td>31</td><td>35</td></tr>
</table></td><td></td><td></td></tr>
<tr><td>Somani 2009</td><td>Qualitative study and systematic</td><td>32</td><td>23 males / 9 female. Mean age=69y (range 41-80). 3 orthotopic bladder replacement, 29 ileal conduit</td><td>N/A qualitative pre-operative interview study using the</td><td>N/A</td><td>N/A</td><td>Mean QoL score 74.8 (range 45-98) on a scale of 1-100 (higher better)</td><td></td><td></td></tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
UK	review		diversions.	schedule for evaluation of individual quality of life-direct weighting (DEIQoL-DW). EORTC QLQ-C30 and satisfaction with life scale (SWLS) assessed pre and 9-12 mo after cystectomy and UD			No patient mentioned body image as an important determinant of QoL.69% thought their appearance would only change a little after surgery. Mean SWLS score improved from 23.4 presurgery to 24.2 postsurgery. EORTC QLQ-C30 =69.2 presurgery and 69 postsurgery. Improved social role and emotional functioning seen post-surgery		
Henningsohn 2002 Sweden	Cross-sectional questionnaire study Patients treated 1977-1995.	484 (48 RT, 175 RC, 261 healthy controls). Excluded patients <65 yrs old.	<table><tr><td></td><td>RC</td><td>RT</td></tr><tr><td>Mean age</td><td>76</td><td>80</td></tr><tr><td>Female</td><td>45 (26%)</td><td>13 (27%)</td></tr><tr><td>Male</td><td>129 (74%)</td><td>35 (73%)</td></tr><tr><td>Conduit diversion</td><td>144 (82%)</td><td>-</td></tr><tr><td>Continent reservoir</td><td>31 (18%)</td><td>-</td></tr><tr><td colspan="3">Pre-op radiation</td></tr><tr><td>40Gy <1978</td><td>18/24 (75%)</td><td></td></tr><tr><td>20Gy >1979</td><td>89/149 (60%)</td><td></td></tr><tr><td>Pre-op chemo</td><td>64/167 (38%)</td><td></td></tr></table>	N/A - Author developed questionnaire assessing urinary tract dysfunction, sexual dysfunction, distress from symptoms, psychological symptoms,	RC vs RT vs control	N/A	**Bowel function:** Most bowel function symptoms were higher in the treated patients compared to controls. Mod or much distress from bowel symptoms was no different between RC and RT groups (39/166 vs 15/47, RR 1.1 (0.6-1.9) **Sexual dysfunction:** In men dissatisfaction with sexual function was lower for RT than RC 36% vs 67% , RR 0.6, 0.4-1.0). Erectile dysfunction 75% RT vs 92% RC (HR 0.8, 0.6-1.0)		

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							No differences in psychological well-being, physical well-being, energy, anxiety, depression.		
Shelley 2001	Systematic review of RCTs published 1976 - 1999	3 trials of 439 patients	All T2-T4 N0M0	Preoperative RT +RC (surgery)	RT followed by salvage RC (radiotherapy)	N/a	**Overall survival:** 3-yr ITT 1.91 (1.30-2.82); 5-yr ITT 1.85 (1.22-2.82) 3-yr treatment received 1.84 (1.17-2.90) 5-yr treatment received 2.17 (1.39-3.38) **Disease-specific survival:** 3-yr ITT 1.65 (0.92-2.95); 5-yr ITT 1.38 (0.75-2.54); 10-yr ITT 1.77 (0.92-3.40) 3-yr treatment received 1.96 (1.06-3.65); 5-yr treatment received 1.78 (0.94-3.37)		Not all patients received protocol treatment after randomisation. Relevance to current practice?
Rodel 2002 Germany	Retrospective series 1982-2000	415 T2-T4 M0	N (415) M/F 327/88 Median age 67 yrs T1, high risk 89 T2 100 T3 195 T4 31 G1/2 197 G3/4 218 N0 331 N+ 28 unknown 56 Resection status R0 118 R1 135 R2 149	126 treated with TUR+RT alone, 302 (since 1985) with TUR+ concomitant radiochemotherapy. Cisplatin or carboplatin. Since 1993 cisplatin + 5-fluorouacil (49 patients). RT used 4-box field technique with median 54Gy to bladder	N/A	Median 36 months, 60 months for surviving patients	**Subsequent treatment:** 20% underwent salvage cystectomy for invasive residual or recurrent tumour **Disease-specific survival:** 5-yr 56%, 10-yr 42% **Overall survival:** 5-yr 51%, 10-yr 31% **Distant mets:** 98 patients. 29% and 35% at 5 and 10 yrs. 5-yr mets free survival 79% with CR tumours but		T category, resection status after initial TUR, age, and lymph vessel involvement were prognostic factors for overall survival.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			Multifocality present: 80 absent: 281 Lymph vessel involvement Present (L1): 175 Absent (L0): 187				52% for residual tumours.		
Shipley 2002 USA	Retrospective series 1986-1997	190 T2-T4	75% male, 25% female, 47% T2, 53% T3-T4a, 14% hydronephrosis, 52% neoadjuvant MCV chemotherapy, 57% visibly complete TURBT.	Bladder conservation reserved for patients with complete response at midpoint in therapy (40Gy), then consolidation by additional concurrent chemo and radiotherapy to 64-65Gy. Incomplete responders advised to have RC. Various schedules of CRT and additional CT were used.	N/A	Median 6.7y for surviving patients (range 2-13.4)	**Overall survival:** 5yr 54%, 10yr 36% **Disease-specific survival:** 5yr 63%, 10y 59%		Age and clinical stage associated with lower OS. Clinical stage and hydronephrosis associated with lower DSS.
Perdona 2008 Italy	Retrospective series 1994-2002	121. Excluded ECOG PS >2, distant mets, prior CT or RT, inadequate haemoglobin, white blood cell count, Scr or bilirubin. All patients refused RC due	N (121) M/F: 90/31 Mean age: 63 yrs (42-77y) T2: 92 T3-T4: 29 G2: 35 G3/4: 86 Concomitant CIS Yes: 12 No: 109	All received neoadjuvant cisplatin-based CT (MCV). EBRT with CT images from a linear accelerator using 4-box field technique. Median dose to pelvis 65Gy and median 65Gy to bladder. From 1998	N/a	Median 66 months (range 6-182)	**Subsequent treatment:** 20% salvage RC for invasive residual or recurrent tumour **Overall survival:** 68% **Disease-specific survival:** 74% **Toxicity:** 4 cardiopulmonary events during neoadjuvant CT. 16% thrombocytopenia,		OS and DSS better in RCT treated patients compared to RT only

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
		to desire to preserve QoL.	Hydronephrosis Yes 10 No 111 Visibly complete TURB present 98 absent 23	concomitant CT (cisplatin or carboplatin) was given during 1st and 5th week of RT			12% cystitis, 12% enteritis.		
Chamie 2008 USA	Retrospective series 1992-2004	10807 - 8034 RC, 2773 RT with MIBC TCC		RC (n=8034) with or without RT. PLND defined as ≥10 lymph nodes	Bladder preservation (n=2773) – TURBT or PC and RT	Not reported	**Overall survival:** <60yrs median OS = 74 mo after RC, 28 mo after RT (HR 1.64, 1.34-1.99); 60-69yrs median OS 49mo RC, 24 mo RT (HR 1.54, 1.34-1.76). 70-79yrs 33mo RC, 19mo RT (HR 1.52, 1.38-1.66); >79yrs 18mo vs 15mo (HR 1.32, 1.19-1.46) **Disease-specific survival:** Patients with RC better than RT regardless of age. 60-69 yrs median = 141mo vs 42mo (HR 1.55, 1.32-1.83); 70-79yr 132 vs 40mo (HR 1.31, 1.16-1.48); >79yrs, 37mo v 22mo (HR 1.21, 1.07-1.38)	n/a	No coding in database for CT. RC with or without RT. The very elderly with no PLND had no overall survival benefit over those who had BP/RT.
Rink 2012 Multicentre	Retrospective series 1979-2008	3088 lymph node negative. No distant mets at time of surgery. Excluded those with LN metastases	N (%) Median age 67 yrs Male 2473 (80) Female 615 (20) pT-stage T0 210 (6.8) Ta-Tis-T1 1037 (33.6)	Radical cystectomy with PLND. No preoperative RT or CT.	n/a	Median 47 months (IQR 70)	**Recurrence-free survival:** 3,5,10 yr = 74%, 70% and 66%. **Cancer-specific survival:** 3,5,10 yr = 80%, 76%, 69%		Pathologic stage, grade, soft tissue surgical margin, lymphovascular invasion were predictive of recurrence and cancer-specific

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			T2 822 (26.6) T3 776 (25.1) T4 243 (7.9 Grade 1 70 (2.3) Grade 2 1393 (45) Grade 3 1415 (45.8) CIS present 1576 (51) CIS absent 1512 (49) Soft tissue surgical margins Negative 3003 (97) positive 85 (2.8)						mortality.
Otto 2012 Germany	Retrospective series 1989-2008	2483 with no distant mets at time of surgery (M0)	N (%) Median age 66.4 Male 1976 (80) female 507 (20) pT stage ≤pT1 708 (28.5) T2a 471 (19) T2b 198 (8) T3a 563 (22.7) T3b 278 (11.2) T4a 228 (9.2) T4b 37 (1.5) pN0 1843 (74.2) pN+ 640 (25.8) LVI present 876 (35.3) Adjuvant chemo 2138 (86)	Radical cystectomy including bilateral LND. No neoadjuvant CT or neoadjuvant or adjuvant RT.	n/a	42 months (IQR 21-79)	**Cancer-specific survival:** 1, 3, 5, 10 years = 88%, 72%, 65% and 57% CSS was higher in males than females (p=0.005) Women showed significantly lower peri-operative mortality after 30 days (1.4% vs 3.2%) and 90 days (2.2% vs 4.6%)		Tumour stage≥pT3, positive LN status older age and female gender were associated with lower CSS

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Hautmann 2012

Germany</td>
<td>Retrospective series

1986-2009</td>
<td>1100 with no distant mets. TCC, no positive surgical margins</td>
<td>
<table>
<tr><td></td><td>N (%)</td></tr>
<tr><td>Median age</td><td>65 yr (23-91)</td></tr>
<tr><td>Male</td><td>892 (81)</td></tr>
<tr><td>Females</td><td>208 (18.9)</td></tr>
<tr><td>pT0 cystectomy</td><td>208 (18.9)</td></tr>
<tr><td colspan="2">Max tumour stage TURBT + RC</td></tr>
<tr><td>pTa/is/T1 N0M0</td><td>284 (25.8)</td></tr>
<tr><td>pT2/a/b N0M0</td><td>403 (36.6)</td></tr>
<tr><td>pT3a/bN0M0</td><td>157 (14.3)</td></tr>
<tr><td>pT4a/b N0M0</td><td>56 (5.1)</td></tr>
<tr><td>pTall N+ M0</td><td>200 (18.2)</td></tr>
</table>
</td>
<td>Radical cystectomy with bilateral PLND. No neoadjuvant or adjuvant RT and/or CT</td>
<td>n/a</td>
<td>Median 38 months (range 0-282)</td>
<td>30-day mortality: 3.2% (n=36) – 6 pulmonary embolism, 4 myocardial infarction, 2 stroke, 3 acute respiratory distress, 14 septicmia.
Overall survival: 10-yr =44.3%
Recurrence-free survival: 10-yr=65.5%
Disease-specific survival: 10-yr =66.8%</td>
<td></td>
<td>Increasing pathologic stage and LN-positive disease associated with higher recurrence and worse OS.</td>
</tr>
</table>

4.2.2 Optimal radical radiotherapy regimen

Review question: What is the optimal radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer?

Rationale

Muscle-invasive bladder cancer can be cured using external beam radiotherapy or surgery with 5 year survival rates of 50-60%. The two treatments have not been compared head-to-head in a randomised control trial. Within the UK, there is variation in radiotherapy schedules used to treat bladder cancer. The two most common schedules are 52.5-55 Gy in 20 fractions over 4 weeks and 64Gy in 32 fractions over 6.5 weeks. The two schedules have never been directly compared and to date, radiotherapy trials in the UK have included both regimes. The most common side effects during treatment are urinary frequency, discomfort, diarrhoea, nausea and tiredness. In the long term, there is a small risk of reduced bladder volume, continuing bowel symptoms, haematuria, loss of reproductive capacity, vaginal stenosis in women and impotence in men. Treatment side-effects and disease-outcome are considered to be comparable between the two protocols. Although many UK centres now treat potentially curative patients with radiotherapy and a radiosensitiser, there are a group of patients who are not fit or able to tolerate radiosensitisation. These patients are treated with radical radiotherapy alone as their definitive treatment.

The addition of chemotherapy or hypoxic modifying agents have been tested in both phase II and III studies, and have found to improve clinical outcomes by 5-10% compared to radiotherapy alone. The improved clinical outcome may be associated with an increase in toxicity. A number of different agents have been used in combination with radiotherapy to increase radiosensivity. The most commonly used agents are mitomycin C and 5-Fluorouracil, carbogen and nicotinamide, gemcitabine and cisplatin. The two largest RCTs have been undertaken in the UK in the last ten years: BC2001 and BCON. BC2001 compared radiotherapy alone versus radiotherapy with mitomycin C and 5-Fluorouracil. BCON compared radiotherapy alone with radiotherapy and carbogen and nicotinamide. Alongside these studies, the UK also recruited to a multicentre phase II study with gemcitabine during radiotherapy. However, the different radiosensitisers have not been directly compared with each other in the context of a randomised control trial. Variation exists within UK practice due to the differences in ease of delivery, cost and toxicity of the different regimes. The different radiotherapy/chemoradiotherapy regimes have resource implications and any differences in outcomes between the two regimes would be of importance. Some patients have to travel long distances for treatment.

This review should aim to establish the optimum radiotherapy and chemoradiotherapy regimes which benefit patients with muscle-invasive bladder cancer by exploring which doses and fractionation maximise clinical outcomes while minimising side-effects. If possible, the review should aim to define which patients are most suitable radiotherapy alone or radiotherapy with radiosensitisation.

Question in PICO format

Population	Intervention	Comparison	Outcomes

Patients offered radical radiotherapy for bladder cancer	Chemoradiotherapy Hypoxic-sensitisation	Radical radiotherapy Various regimens (e.g. dose, duration of treatment)	• Overall survival • Disease-free survival • Treatment-related morbidity • Treatment-related mortality • Health-related quality of life, inc patient reported outcomes • Metastases free survival

METHODS

Information sources

A literature search was performed by the information specialist (EH)

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. Comparative data was obtained for this review.

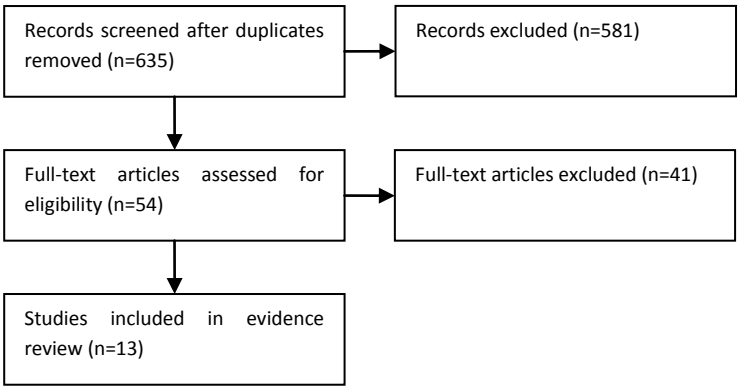
Data synthesis

Dichotomous data from comparative studies were extracted into RevMan and risk ratios were calculated where possible.

RESULTS

Result of the literature searches

Figure 69. Study flow diagram



Study quality and results

Evidence is summarised in Tables 108-116.

Evidence statements

Radiotherapy with carbogen and nicotinamide (RT+CON) versus radiotherapy alone

Moderate quality evidence from one randomised trial (Hoskin, et al., 2009/2010) of 333 participants suggests that there is a 13% improvement in three-year overall survival from 46% to 59% in favour of RT+CON compared to radiotherapy alone (HR 0.85, 95% CI 0.73 to 0.99). There was an 11% increase in relapse-free survival at three years in favour of RT+CON (43% vs 54%), although the confidence interval of the hazard ratio includes the null value, suggesting uncertainty of a difference between groups (HR 0.86, 95% CI 0.74 to 1.00). Rates of urinary (39% and 32%) and GI (7% and 5%) complications were similar between groups. Larger doses per fraction did not increase bladder or bowel morbidity. Two deaths (1.2%) were considered due to RT+CON and one death (0.6%) to radiotherapy alone.

Chemoradiotherapy (CRT) with 5-fluorouacil and mitomycin C versus radiotherapy alone

Moderate quality evidence from one randomised trial (James et al., 2013) of 360 participants suggests that loco-regional disease free survival is better with chemoradiotherapy (mitomycin C and 5-fluorouacil) compared to radiotherapy alone, with two-year recurrence free rates of 67% versus 54% (HR 0.68, 95% CI 0.48 to 0.96). The chemoradiotherapy effect did not vary significantly between radiotherapy type or dose fractionation or with neoadjuvant chemotherapy. Overall there were 98 deaths in the chemoradiotherapy group and 110 in the radiotherapy group, with an absolute difference in five-year survival of 7% (95% CI, -3% to 17%) in favour of chemoradiotherapy, although the confidence interval of the hazard ratio includes the null value, suggesting uncertainty of a difference between groups (HR 0.82, 95% CI 0.63 to 1.09). There was also uncertainty of a difference between groups in terms of disease-specific survival (HR 0.77, 95% CI 0.57 to 1.05) and disease-free survival (0.78, 95% CI 0.6 to 1.03). Metastases-free survival was better in the chemoradiotherapy group, with an improvement of 11.3% (0.4% to 21.1%) at five years (HR 0.72, 95% CI 0.53 to 0.99). Acute grade three or four toxic effects were increased in the chemoradiotherapy groups compared to radiotherapy alone (36% vs 27.5%), although the risk ratio includes the null value suggesting uncertainty of a difference between groups (RR 1.31, 95% CI 0.96 to 1.78). Grade three or four RTOG late events occurred at some point during follow-up in 8.3% (10/120) of the chemoradiotherapy group and 15.7% (17/108) of the radiotherapy group (RR 0.53, 95% CI 0.25 to 1.11). Very low quality evidence from one observational study of 50 patients treated with chemoradiotherapy (cisplatin and 5-fluorouracil) reports that mean scores for global quality of life and subscales were slightly improved six months after treatment and were maintained at over 70% (best quality of life score is 100%) for all patients alive without relapse.

Moderate quality evidence from the BC2001 trial reported in Huddart et al. (2013) suggest that rates of late side-effects were not significantly different between patients receiving reduced high-dose volume radiotherapy and standard whole-bladder radiotherapy (OR 1.34, 95% CI 1.42 to 4.28). The effect estimates for time to locoregional recurrence (HR 0.80, 95% CI 0.51 to 1.26) and overall survival (HR 0.82, 95% 0.58 to 1.16) also suggest uncertainty of a difference between treatment groups.

Accelerated fractionation (AF) versus conventional fractionation (CF) radiotherapy

Moderate quality evidence from one randomised trial of 229 participants suggests that there was no difference in relapse-free survival, overall survival, and local failure between accelerated fractionation (60.8Gy in 32 fractions over 26 days) and conventional fractionation (64Gy in 32 fractions over 45 days). At five years overall survival was 37% for AF and 40% for CF. There were two treatment related deaths, both on the AF arm. Acute grade two or three RTOG bowel toxicity was reported in 44% of AF patients compared to 26% of CF patients (RR 1.68, 95% CI 1.14 to 2.49). Late radiation toxicity was reported in 44% of the AF group and 35% of the CF group (RR 1.26, 95% CI 0.91 to 1.76).

Neoadjuvant MVC and RT versus concurrent cisplatin CRT

Very low quality evidence from one observational study reported that five-year overall survival was 73% for patients treated with either neoadjuvant chemotherapy and radiotherapy (n=41) or concurrent radiotherapy (n=39), with no difference between treatment protocols. There were also no differences between protocols for cancer-specific survival and distant metastases. Disease-free survival was improved with concurrent chemoradiotherapy compared to neoadjuvant chemotherapy (82% versus 67%). There were no differences in GI complications, although urinary toxicity was higher in the concurrent chemoradiotherapy group (33% versus 12%, RR 0.37, 95% CI 0.14 to 0.93).

Neoadjuvant MVC + RT versus Neoadjuvant MVC + Concurrent platinum-based CRT

Very low quality evidence from one observational study suggests that overall survival and disease-specific survival are improved with neoadjuvant chemotherapy and concurrent chemoradiotherapy compared to neoadjuvant chemotherapy and radiotherapy alone. There were no significant differences between treatment protocols in terms of acute grade three or four bone marrow (16% overall), bladder (12% overall), or intestinal (12% overall) toxicity.

RT only versus Concurrent CRT

Very low quality evidence from one observational study reported on 473 patients with a median overall survival of 28.5 months in patients treated with RT compared to 70 months in those treated with concurrent chemoradiotherapy. One quality of life study including 48 long-term survivors after trimodality therapy reported that the mean physical functioning score was 89 (possible range 0-100) and the general health perceptions score was 74 (possible range 0-100). This suggests that global health-related quality of life is good in this population (very low quality evidence).

Conventional single-phase RT to whole bladder versus two-phase reduced volume treatment

One observational study (very low quality evidence) comparing conventional single phase radiotherapy with a two-phase technique limiting the high-dose area reported that median overall survival was 2.8 years with both techniques (HR 0.91, 95% CI 0.64 to 1.3). The two-phase treatment was associated with a lower rate of overall grade 3 to 4 late toxicity (44% versus 25%, RR 0.56, 95% CI 0.33 to 0.95), and fewer acute bladder and bowel toxicities.

Concomitant CRT with Gemcitabine versus RT alone

One very low quality study of 69 patients reported three year overall survival of 38% with concurrent chemoradiotherapy with gemcitabine and 27% with radiotherapy alone. One quality of life study of

23 patients treated with concurrent gemcitabine and radiotherapy reported that there were no statistically significant changes in general quality of life scores before, during or after treatment.

Table 108. GRADE evidence profile: Radiotherapy with carbogen and nicotinamide (RT+CON) versus radiotherapy alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT+CON	RT alone	Relative (95% CI)	Absolute	
Overall survival (mortality rate; follow-up median 57-60 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	85/164 (51.8%)	100/163 (61.3%)	HR 0.85 (0.73 to 0.99)	3-yr OS 59% vs 46% in favour of RT+CON	⊕⊕⊕O MODERATE
Relapse-free survival (time to tumour recurrence in bladder (MIBC only), locoregional failure or death; follow-up median 57-60 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	N=164	N=163	HR 0.86 (0.74 to 1.00)	3-yr RFS 54% vs 43% in favour of RT+CON	⊕⊕⊕O MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	none	serious[2]	none	2/164 (1.2%)	1/163 (0.6%)	-	-	⊕⊕⊕O MODERATE
Grade 3 or worse urinary complications (assessed with: LENT/SOMA, 3yr incidence)											
1[1]	randomised trials	none	none	none	serious[2]	none	39%	32%	-	No significant difference (p=.4)	⊕⊕⊕O MODERATE
Grade 3 or worse GI complication (assessed with: LENT/SOMA, 3yr incidence)											
1[1]	randomised trials	none	none	none	serious[2]	none	7%	5%	-	No significant difference (p=.5)	⊕⊕⊕O MODERATE
Grade 1 or worse nausea/vomiting (assessed during first 7 weeks)											
1[1]	randomised trials	none	none	none	serious[2]	none	23-41%	6-12%	-	-	⊕⊕⊕O MODERATE
Health-related quality of life											
0	No evidence available										

[1] Hoskin 2009/2010 (BCON trial)

[2] Low number of events limits precision

[3] Confidence interval includes null value

Table 109. GRADE evidence profile: Chemoradiotherapy (CRT) with 5-fluorouacil and mitomycin C versus radiotherapy alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT	RT	Relative (95% CI)	Absolute	
Locoregional disease-free survival (rate of recurrence in pelvic nodes or bladder; follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	55/182 (30.2%)	76/178 (42.7%)	HR 0.68 (0.48 to 0.96)	2yr recurrence-free rate 67% vs 54% in favour of CRT	⊕⊕⊕O MODERATE
Invasive locoregional disease-free survival (follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	182	178	HR 0.57 (0.37 to 0.9)	2yr relapse rate 32% vs 18% in favour of CRT	⊕⊕⊕O MODERATE
Overall survival (any cause mortality rate; follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	98/182 (53.8%)	110/178 (61.8%)	HR 0.82 (0.63 to 1.09)	5yr OS rate 48% vs 35%, absolute difference 7% (-3 to 17%)	⊕⊕⊕O MODERATE
Disease-specific survival (mortality from bladder cancer; follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	74/182 (40.7%)	92/178 (51.7%)	HR 0.77 (0.57 to 1.05)	Uncertainty of difference between groups	⊕⊕⊕O MODERATE
Disease-free survival (follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	95/182 (52.2%)	113/178 (63.5%)	HR 0.78 (0.6 to 1.03)	Uncertainty of difference between groups	⊕⊕⊕O MODERATE
Metastasis-free survival (rate of metastasis; follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	71/182 (39%)	94/178 (52.8%)	HR 0.72 (0.53 to 0.99)	In favour of CRT	⊕⊕⊕O MODERATE
Grade 3-4 acute toxic effects (assessed with: NCI CTCAE during treatment)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	64/178 (36%)	50/182 (27.5%)	RR 1.31 (0.96 to 1.78)	85 more per 1000 (from 11 fewer to 214 more)	⊕⊕⊕O MODERATE
Grade 3-4 late RTOG events (assessed >6 months after randomisation)											
1	randomised trials	none	none	none	serious[2,3]	none	10/120 (8.3%)	17/108 (15.7%)	RR 0.53 (0.25 to 1.11)	74 fewer per 1000 (from 118 fewer to 17 more)	⊕⊕⊕O MODERATE
Grade 3-4 late LENT/SOMA toxicity (assessed >6 months after randomisation)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	29/77 (37.7%)	22/75 (29.3%)	RR 1.28 (0.82 to 2.02)	82 more per 1000 (from 53 fewer to 299 more)	⊕⊕⊕O MODERATE
Treatment-related mortality											
0	No evidence										
Health-related quality of life (EORTC QLQ-C30 in patients alive without cystectomy or disease; scale 0-100, higher scores are better)											
1[4]	observational study	none	none	none	serious[2]	none	N=50[5]				⊕OOO VERY LOW

[1] James 2012 (BC2001 trial); [2] Low number of events limits precision; [3] Confidence interval includes null value; [4] Lagrange 2011; [5] Mean score for global QoL and for physical, emotional, personal, cognitive, and social functions were slightly improved 6 months after treatment and were maintained over 70% (scale 0% (worst) to 100% (best)) for all patients alive without relapse.

Table 110. GRADE evidence profile: Reduced high-dose volume versus standard volume radiotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reduced high-dose volume	Standard volume	Relative (95% CI)	Absolute	
Locoregional recurrence-free survival (follow-up median 72.7 months; assessed with: recurrence in pelvic nodes or bladder)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	35/111 (31.5%)	41/108 (38%)	HR 0.80 (0.51 to 1.26)	2-year rate 64%vs 61%	⊕⊕⊕O MODERATE
Overall survival (follow-up median 72.7 months; assessed with: any cause mortality)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	62/111 (55.9%)	71/108 (65.7%)	HR 0.82 (0.58 to 1.16)	5-year survival 44% vs 38%	⊕⊕⊕O MODERATE
Grade 3/4 acute toxicity (assessed with: NCI CTCTAE during treatment)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	19/95 (20%)	30/120 (25%)	OR 0.79 (0.33 to 1.87)	42 fewer per 1000 (from 151 fewer to 134 more)	⊕⊕⊕O MODERATE
Any Grade 3/4 RTOG toxicity at any time during follow-up											
1[1]	randomised trials	none	none	none	serious[2,3]	none	12/67 (17.9%)	11/85 (12.9%)	OR 1.34 (1.42 to 4.28)	37 more per 1000 (from 45 more to 259 more)	⊕⊕⊕O MODERATE
Any Grade 3/4/ LENT-SOM toxicity at anytime during follow-up											
1[1]	randomised trials	none	none	none	serious[2,3]	none	35/61 (57.4%)	38/78 (48.7%)	OR 1.65 (0.67 to 4.06)	123 more per 1000 (from 98 fewer to 307 more)	⊕⊕⊕O MODERATE
Metastases-free survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Huddart 2013 (BC20001 trial)

[2] Low number of events limits precision

[3] Wide confidence intervals limits precision

Table 111. GRADE evidence profile: Accelerated fractionation versus conventional fractionation radiotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AF	CF	Relative (95% CI)	Absolute	
Relapse-free survival											
1[1]	randomised trials	none	none	none	serious[2,3]	none	68/129 (52.7%)	49/100 (49%)	HR 1.00 (0.69 to 1.45)	5-yr RFS 39% AF vs 32% CF, uncertainty of difference	⊕⊕⊕O MODERATE
Overall survival (mortality rate)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	74/129 (57.4%)	56/100 (56%)	RR 1.02 (0.81 to 1.29)	5-yr OS 37% AF vs 40% CF, uncertainty of difference	⊕⊕⊕O MODERATE
Local failure											
1[1]	randomised trials	none	none	none	serious[2,3]	none	41/129 (31.8%)	29/100 (29%)	RR 1.17 (0.79 to 1.73)	2-yr local control 68% AF vs 65% CF, uncertainty of difference	⊕⊕⊕O MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	none	serious[2,3]	none	2/129 (1.6%)	0/100 (0%)	RR 3.88 (0.19 to 80.02)	-	⊕⊕⊕O MODERATE
Late radiation toxicity											
1[1]	randomised trials	none	none	none	serious[2,3]	none	57/129 (44.2%)	35/100 (35%)	RR 1.26 (0.91 to 1.76)	91 more per 1000 (from 31 fewer to 266 more)	⊕⊕⊕O MODERATE
Acute bowel toxicity (assessed with: Grade 2-3 RTOG)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	53/121 (43.8%)	25/96 (26%)	RR 1.68 (1.14 to 2.49)	177 more per 1000 (from 36 more to 388 more)	⊕⊕⊕O MODERATE
Acute bladder toxicity (assessed with: Grade 2-3 RTOG)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	42/121 (34.7%)	34/96 (35.4%)	RR 0.98 (0.68 to 1.41)	7 fewer per 1000 (from 113 fewer to 145 more)	⊕⊕⊕O MODERATE
Health-related quality of life											
0	No evidence available										

[1] Horwich 2005

[2] Low number of events limits precision

[3] Confidence interval includes null value

Table 112. GRADE evidence profile: Neoadjuvant MVC and RT versus Concurrent cisplatin CRT

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant CT+RT, n=41	Concurrent CRT, n=39	Relative (95% CI)	Absolute	
Overall survival (follow-up median 72 months)											
1[1]	observational studies	none	none	none	serious[2]	none	5-yr OS 73% not reported separately		-	No difference between protocols (p=.820)	⊕OOO VERY LOW
Cancer-specific survival (follow-up median 72 months)											
1[1]	observational studies	none	none	none	serious[2]	none	5-yr CSS 82% not reported separately		-	No difference between protocols (p=.688)	⊕OOO VERY LOW
Distant metastases (follow-up median 72 months)											
1[1]	observational studies	none	none	none	serious[2]	none	Rate not reported		-	No difference between protocols (p value not reported)	⊕OOO VERY LOW
Disease-free survival (follow-up median 72 months)											
1[1]	observational studies	none	none	none	serious[2]	none	67%	82%	-	Favours CRT (p=.031)	⊕OOO VERY LOW
Urinary toxicity, Grade 2 or higher (assessed with: RTOG)											
1[1]	observational studies	none	none	none	serious[2]	none	5/41 (12.2%)	13/39 (33.3%)	RR 0.37 (0.14 to 0.93)	210 fewer per 1000 (from 23 fewer to 287 fewer)	⊕OOO VERY LOW
GI toxicity Grade 2 or higher (assessed with: RTOG)											
1[1]	observational studies	none	none	none	serious[2]	none	5/80 (6%) Rate not reported separately		-	No difference between protocols	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										

[1] Zapatero 2012

[2] Low number of events limits precision

Table 113. GRADE evidence profile: Neoadjuvant MVC + RT versus Neoadjuvant MVC + Concurrent platinum-based CRT

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT n=43	CRT n=78	Relative (95% CI)	Absolute	
5-year Overall survival (follow-up median 66 months)											
1[1]	observational studies	none	none	none	serious[2]	none	60.4%	71.8%	-	Favours CRT (p=.008)	⊕OOO VERY LOW
5-year Disease-specific survival (follow-up median 66 months)											
1[1]	observational studies	none	none	none	serious[2]	none	62.8%	79.4%	-	Favours CRT (p=.003)	⊕OOO VERY LOW
Acute toxicity: bone marrow (assessed with: WHO criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	6/43 (14%)	13/78 (16.7%)	RR 0.84 (0.34 to 2.04)	27 fewer per 1000 (from 110 fewer to 173 more)	⊕OOO VERY LOW
Acute toxicity: bladder (assessed with: WHO criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	6/43 (14%)	9/78 (11.5%)	RR 1.21 (0.46 to 3.17)	24 more per 1000 (from 62 fewer to 250 more)	⊕OOO VERY LOW
Acute toxicity: intestinal (assessed with: WHO criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	4/43 (9.3%)	11/78 (14.1%)	RR 0.66 (0.22 to 1.95)	48 fewer per 1000 (from 110 fewer to 134 more)	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										
Metastases-free survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										

[1] Perdona 2008

[2] Low number of events limits precision

Table 114. GRADE evidence profile: RT only versus Concurrent CRT

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT, n=142	CRT, n=331	Relative (95% CI)	Absolute	
Overall survival (follow-up median 71.5 months)											
1[1]	observational studies	serious[2]	none	none	serious[3]	none	Median OS 28.5 months	Median OS 70 months	-	Favours CRT (p<0.001)	⊕OOO VERY LOW
Disease-free survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Metastases-free survival											
0	No evidence available										
Urinary function (lacking control in previous 7 days)											
1[4]	observational studies	none	none	none	serious[5]	none	n/a	9/48 (19%)	-	-	⊕OOO VERY LOW
Bowel function (difficulty in control in previous 7 days)											
1[4]	observational studies	none	none	none	serious[5]	none	n/a	10/48 (22%)	-	-	⊕OOO VERY LOW
Quality of life (measured with: SF-36; Physical functioning overall mean; range of scores: 0-100; Better indicated by higher values)											
1[4]	observational studies	none	none	none	serious[5]	none	n/a	Mean=89	-	-	⊕OOO VERY LOW
Quality of life (measured with: SF-36; General health perceptions; range of scores: 0-100; Better indicated by higher values)											
1[4]	observational studies	none	none	none	serious[5]	none	n/a	Mean=74	-	-	⊕OOO VERY LOW

[1] Krause 2011

[2] Patient characteristics not reported separately for treatment protocols. Unclear if groups were comparable at baseline.

[3] Low number of events limits precision

[4] Zietman 2003

[5] Small sample size limits precision

Table 115. GRADE evidence profile: Conventional single-phase RT to whole bladder versus two-phase reduced volume treatment

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Two-phase RT, n=75	Conventional RT, n=154	Relative (95% CI)	Absolute	
Overall survival (follow-up median 4.8 years)											
1[1]	observational studies	none	none	none	serious[2,3]	none	Median OS 2.8y	Median OS 2.8y	HR 0.91 (0.64 to 1.3)	-	⊕OOO VERY LOW
Disease-free survival											
0	No evidence available										
Metastases-free survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Grade 3 incontinence risk at 5-yr (assessed with: RTOG criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	19%	30%	HR 0.41 (0.2 to 0.81)	Favours two-phase RT	⊕OOO VERY LOW
Overall Grade 3-4 late effects (assessed with: RTOG criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	13/53 (24.5%)	42/96 (43.8%)	RR 0.56 (0.33 to 0.95)	Favours two-phase RT, 19% reduction in late effects	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Mangar 2006

[2] Small sample size limit precision

[3] Confidence interval includes null value

Table 116. GRADE evidence profile: Concomitant CRT with Gemcitabine versus RT alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT	RT	Relative (95% CI)	Absolute	
Overall survival (follow-up median 18 months)											
1[1]	observational studies	none	none	none	serious[2]	none	N =23 3-yr OS 38%	N=46 3-yr OS 27%	Not reported	-	⊕OOO VERY LOW
Disease-free survival											
0	No evidence available										
Metastases-free survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Increased urine frequency during treatment (assessed with: FACT-BL)											
1[3]	observational studies	none	none	none	serious[2]	none	11/13 (85%)	n/a	-	-	⊕OOO VERY LOW
Health-related quality of life (measured with: FACT-BL and FACT-G; Better indicated by lower values)											
1[3]	observational studies	none	none	none	serious[2]	none	N=23	n/a	-	No significant change before, during or after treatment	⊕OOO VERY LOW

[1] Asadauskiene 2010

[2] Small sample size limits precision

[3] Herman 2004

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Evidence tables

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
James 2012 UK BC2001 trial	Randomised trial 2001-2008	360 in ITT analysis. At least 18yrs with T2-T4aN0M0 BCa. PS 0-2, adequate WBC, platelet count. Excluded pregnancy, previous cancer or RT likely to interfere with protocol or inflammatory bowel disease	N (%) Whole bladder RT (randomised) 63 (17.5) Modified volume RT 58 (16.1) Whole bladder RT (not randomised) 239 (66.4) Male 289 (80.3) Female 71 (19.7) WHO PS 0 232 (64.4) WHO PS 1 117 (32.5) WHO PS 2 11 (3.1) Median age 71.9 yr pT stage 1 1 (0.3) 2 297 (82.5) 3a 25 (6.9) 3b 22 (6.1) 4a 14 (3.9) unknown 1 (0.3) TCC 352 (97.8) Tumour resection Not resected 9 (2.5) Biopsy 31 (8.6) Complete resection 198 (55) Incomplete 115 (31.9) Residual mass after resection Yes 100 (27.8) No 239 (66.4) Neoadjuvant CT planned Yes 118 (32.8) No 242 (67.2) Planned RT schedule 55 Gy in 20 fractions 142 (39.4) 64 Gy in 32 fractions 217 (60.3)	Radiotherapy with synchronous chemotherapy (ITT n=182) with fluorouracil and MMC. Whole bladder or modified volume RT to uninvolved bladder Fluorouracil administered as continuous infusion (500mg per m^2 of body surface area per day) during fractions 1-5 and 16-29 of RT (10 days total). MMC added as iv bolus dose of 12mg per m^2 on day 1.	Radiotherapy alone (ITT n=178) 2 schedules permitted – 55Gy in 20 fractions over 4-week period or 64 Gy in 32 fractions over 6.5 wk period	Median 69.9mo (IQR 50.1 to 84.1)	**Loco-regional disease-free survival:** 2-yr rates 67% in CRT group vs 54% in RT group (HR 0.68, 95% CI 0.48 to 0.96). HR after adjustment for neoadjuvant chemo, age, RT dose, tumour stage, PS, tumour grade = 0.66 (95% CI 0.46 -0.95). The CT effect did not vary significantly between the RT subgroups or with neo-adjuvant therapy **Overall survival:** 98 deaths in CRT and 110 with RT. 5-yr overall survival 48% CRT vs. 35% RT, absolute difference of 7%. HR for overall survival =0.82 (0.63-1.09) **Disease-specific survival:** 74 deaths from BCa with CRT, 92 with RT. HR=0.77 (0.57-1.05) **Disease-free survival:** 95 CRT v 113 RT, HR=0.78	CRUK and NIH	Unblinded trial. Adequate randomisation. Reasons for withdrawal provided. Data from this trial comparing whole-bladder vs reduced high-dose volume radiotherapy reported in Huddart (2013)

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>(0.60-1.03)
Metastases-free survival: 71 CRT v 94 RT, HR=0.72 (0.53-0.99)
Adverse events:
G3-4 toxic effects 64/178 (36%) CRT vs 50/182 RT (27.5%) p=0.07
GI toxicity 17 (9.6%) CRT vs. 5 (2.7%) RT. G3-4 RTOG events 10/120 (8.3%) CRT vs. 17/108 (15.7%) RT.
G3/4 LENT/SOM toxicity 29/77 (37.7%) CRT vs. 22/75 (29.3%) RT.</td><td></td><td></td></tr>
<tr><td>Huddart 2013
UK
BC2001 trial</td><td>Randomised trial
2001-2006</td><td>At least 18yrs with with T2-T4aN0M0 BCa. PS 0-2, adequate WBC, platelet count. Excluded pregnancy, previous cancer or RT likely to interfere with protocol or inflammatory bowel disease</td><td><table><tr><th></th><th>sRT (n=108)</th><th>RHDVRT (n=111)</th></tr><tr><td>Chemo</td><td>29%</td><td>30%</td></tr><tr><td>No chemo</td><td>30%</td><td>23%</td></tr><tr><td>Elect no chemo</td><td>42%</td><td>48%</td></tr><tr><td>Male</td><td>84%</td><td>80%</td></tr><tr><td>Female</td><td>16%</td><td>20%</td></tr><tr><td>Median age</td><td>75%</td><td>73%</td></tr><tr><td>WHO PS0</td><td>53%</td><td>51%</td></tr><tr><td>pT2</td><td>87%</td><td>81%</td></tr><tr><td>Grade 3</td><td>79%</td><td>84%</td></tr><tr><td>TCC</td><td>98%</td><td>98%</td></tr><tr><td>Multiple tumours</td><td>5%</td><td>4%</td></tr><tr><td>Complete resection</td><td>52%</td><td>57%</td></tr><tr><td>Incomplete resection</td><td>36%</td><td>32%</td></tr></table></td><td>Reduced high-dose volume radiation therapy (RHDVRT)

For RHDVRT patients, 2 PTVs were defined: PTV1 as for the sRT group, and PTV2 as gross tumor volume (ie, tumor seen on MRI/CT with guidance of surgical bladder map) plus a 1.5-cm margin. Three-dimensional</td><td>Standard whole-bladder radiation therapy (sRT)

For sRT the planning target volume (PTV) was the outer bladder wall plus the extravesical extent of tumor with a 1.5 cm margin. An anterior and 2 lateral fields were used to encompass the PTV in the 95% isodose.

Radiotherapy (CT planned)-
2 schedules</td><td>Median 72.7 months (IQR 61 to 90)</td><td>Acute toxicity (CTC): Grade 3-4 toxicity in 49/215 (23%) patients with no difference between groups.
Late radiotherapy related side effects (at 1 and 2 yrs): No differences between groups. 1 yr Grade 3-4 GU toxicity 2/54 (3.7%) sRT and 1/53 (1.9%) RHDVRT
2 yr 1/42 (2.4%) sRT and 2/37 (5.4%) RHDVRT

Locoregional recurrence-free</td><td>CRUK and NIH</td><td>Radiation volume randomisation closed early due to poor recruitment. Non-inferiority could not be formally concluded.
Independent randomization. Computer-generated random permuted blocks were used, stratifying by treating center, planned neoadjuvant</td></tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			Residual mass after resection	35%	23%	conformal radiation therapy was used; RHDVRT could be delivered as a concomitant boost. The aim of the RHDVRT treatment was to deliver 100% (±5%) of the reference dose to PTV2 and 80% (±5%) of the reference dose to PTV1 using 3 or 4 coplanar fields	permitted – 55Gy in 20 fractions over 4-week period or 64 Gy in 32 fractions over 6.5 wk period		**survival:** 2-yr rate sRT 61% (95% CI, 50%-71%), RHDVRT 64% (52%-73%) The 95% CI for absolute difference in LRRF rate at 2 years excluded RHDVRT, being 10% worse in the ITT population (RHDVRT improvement 6.4% [−7.3%, 16.8%]) but not in the per-protocol population (RHDVRT improvement 2.6% [−12.8%, 14.6%]); therefore, noninferiority could not be formally concluded. 26 patients (11.9%) (13 sRT, 13 RHDVRT) have undergone cystectomy; time to cystectomy is comparable between treatment groups 23 cystectomies (10 sRT, 13 RHDVRT) were for disease recurrence. **Overall survival:** 5-yr rate 38% sRT vs. 44% RHDVRT (p=0.28)		chemotherapy use, and entry to one or both randomizations.
			Neoadj chemo planned	24%	23%						
			55Gy/20fx	40%	32%						
			64Gy/32fx	59%	68%						
			Full dose RT received	97%	96%						
			No RT delay ≥7d	98%	96%						

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Hoskins 2009/2010 UK	Randomised trial 2000-2006	333 with TCC MIBC or high grade T1 or prostatic invasion, over 18 yrs and able to use closed breathing system. Excluded T4b tumours, distant mets or enlarged pelvic lymph nodes, lung disease, impaired renal or hepatic function, heart disease, vascular disease or use of diuretics or ACE inhibitors	RT / RT+CON Median age: 75 (51-90) / 74 (51-90) Male: 129 (79) / 129 (81) Female: 34 (21) / 30 (19) T1: 14 (9) / 16 (10) T2: 103 (63) / 111 (70) T3: 39 (24) / 27 (17) T4a: 6 (4) / 5 (3) T4b: 1 (0.6) / 0 G1: 0 / 0 G2: 22 (14) / 24 (15) G3: 140 (86) / 134 (84) G4: 0 / 1 (0.6) Pre-RT surgical procedure Complete debulking: 66 (41) / 60 (38) Partial debulking: 43 (26) / 55 (35) Biopsy only: 46 (28) / 41 (26) Not reported: 8 (5) / 3 (2)	Radiotherapy + carbogen and nicotinamide (NAM) Carbogen 2% CO_2 and 98% O_2 through closed breathing system 5min before and during RT. Oral dose 60mg kg^{-1} NAM given 1.5-2h before each fraction. When toxic effects NAM reduced to 40mg	Radiotherapy alone CT planned 3-4 field technique. Either 55 Gy in 20 fractions in 4 wks and 64 Gy in 32 fractions in 6.5 wks. Treatment daily 5x/wk.	Median - 57mo for RT alone or 60mo for RT +CAR/NAM	**Overall survival:** 3-yr rate 59% RT+CON vs. 46% RT alone (HR 0.85 (0.73 to 0.99). Median OS = 30 months RT and 54 months RT+CON. Exclusion of T1 disease increased significance in favour of RT+CON. 100 deaths in RT and 85 in RT+CON. **Relapse-free survival:** 3yr rate 43% RT vs. 54% RT+CON (HR 0.86, 0.74-1.00). **Treatment-related mortality:** 2 (1.2%) RT+CON vs. 1 (0.6%) RT only **Treatment-related morbidity:** Grade 3+ SOMA/LENT. 3yr incidence of urinary events = 39% and 32% (p=.4). GI morbidity 7% RT+CON vs 5% RT alone (p=.5). No evidence that larger doses per fraction increased bladder or bowel morbidity. Grade 1 Nausea/ vomiting during 1st 7wks = 23-41% RT+CON vs 6-12%	CRUK	Adequate randomisation and reasons provided for withdrawals

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							RT only. Severe Urinary frequency 18% RT vs 15% RT+CON. Severe Diarrhoea 3% RT vs. 5% RT+CON		
Horwich 2005 UK	Randomised trial 1988-1998	229 with T2 or T3 BCa. Excluded advanced lymphadenopathy or metastases, severe illness, inflammatory bowel disease, MI, or previous pelvic surgery	<table><tr><td></td><td>ART</td><td>CRT</td></tr><tr><td>N</td><td>129</td><td>100</td></tr><tr><td>Median age</td><td>68 (64-72)</td><td>67 (61-72)</td></tr><tr><td>Male</td><td>107 (83)</td><td>22 (17)</td></tr><tr><td>Female</td><td>22 (17)</td><td>12 (12)</td></tr><tr><td>T1</td><td>1 (1)</td><td>0</td></tr><tr><td>T2</td><td>59 (46)</td><td>49 (50)</td></tr><tr><td>T3</td><td>67 (53)</td><td>49 (50)</td></tr><tr><td>unknown</td><td>2</td><td>2</td></tr></table>	Accelerated RT: 60.8 Gy in 32 fractions over 26 days RT with CT planning and linear accelerator using 3 or 4 field technique.	Conventional RT: 64Gy in 32 fractions over 45 days Both 2 fractions/day with min 6h gap between fractions using 1.8 or 2Gy.		**Relapse-free survival:** 68/129 (53%) AF vs 49/100 (49%) CF. 5yr RFS 38.9% vs 32.8% (HR=1, 0.69-1.45) **Overall survival:** 74/129 (57%) AF vs 56/100 deaths (56%) CF 5yr OS 37.2% vs 39.9% **Local failure:** 41/129 (32%) AF vs 29/100 (29%) CF. 2yr local control rate 68.4% vs 64.9% for AF and CF. **Late radiation toxicity:** 57 (46%) AF vs 35 (39%) CF. 2yr risk 44.3% AF v 37.7% CF (p=0.23) **Acute bowel toxicity (RTOG) Grade 2-3:** 53/121 (44%) AF v 25/96 (26%) CF **Acute bladder toxicity (RTOG) Grade 2-3:** 42/121 (34.7%) AF v 34/96 (36%) CF.	NHS exec, ICR, Bob champion cancer trust, CRUK	
Lagrange 2011	Observational	53	Median age =68y (43-78), 45 male/ 6	Radiotherapy:	N/a	Median 8y	**Quality of life**	Not	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
France	study (prospective) 1999-2001		female 22% T3 or T4a, 96% high grade	45 Gy in 25 fractions over 5 weeks. Concomitant 4-day continuous Cisplatin 20mg/m^2/day and 5-fluorouracil 600mg/m^2/day on wk 1,4,and 7 of RT			**EORTC QLQ-C30:** Mean score for global QoL and for physical, emotional, personal, cognitive, and social functions were slightly improved 6 months after treatment and were maintained over 70% for all patients alive without relapse	reported	
Zapatero 2012 Spain	Observational study (prospective) 1990-2010	80 T2-T4 BCa. Patients had to be eligible for RC and were offered bladder sparing protocol. exclude distant or LN mets, prior pelvic RT, or contraindication for CT.	<table><tr><td></td><td>P1 n=41</td><td>P2 n=39</td></tr><tr><td>Median age</td><td>63</td><td>60</td></tr><tr><td>M/F</td><td>71/9</td><td>37/4</td></tr><tr><td>R0/R1</td><td>27/14</td><td>28/9</td></tr><tr><td>Multiple lesions</td><td>17</td><td>11</td></tr><tr><td>Tis</td><td>1</td><td>5</td></tr><tr><td>Hydronephrosis</td><td>3</td><td>5</td></tr></table>	Protocol 1 (1990-1999): 3 cycles of MVC CT and consolidative RT 60 Gy (2Gy/fraction, 5 fractions/wk) in complete responders. RT 4-6wks after CT. 3D RT planning post 1995.	Protocol 2 (2000-2010): RT 40.8Gy and concurrent Ciplatin CT. Weekly Cisplatin before RT in 34 pts (20mg/m^2). Taxol in 5 pts with mild renal insufficiency (50mg/m^2). AHFRT in 24 pts, 15 normofractionated RT 64-66Gy. Consolidation RT in responders 1.5Gy twice daily to 24 Gy with CT. Total dose 64.8Gy to bladder and 45.6Gy to LNs.	Median 72mo (range 9-204)	**Overall survival:** 5- and 10- yr for all pts = 73% and 60%, no difference between protocols (p=.820) **Cancer-specific survival:** 5- and 10-yr for all pts = 82% and 80%, no difference between protocols (p=.688) **Distant metastasis:** No difference between protocols. **Disease-free survival:** Higher for P2 (85% v 67%, p=.031) **Urinary toxicity (RTOG):** 13/39 (33%) P2 vs 5/41 (12%) P1. **GI toxicity ≥Grade 2:** no difference between protocols	No financial interests declared by authors	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Perdona 2008 Italy	Retrospective series 1994-2002	121. Excluded ECOG PS >2, distant mets, prior CT or RT, inadequate haemoglobin, white blood cell count, Scr or bilirubin. All patients refused RC due to desire to preserve QoL.	<table><tr><td></td><td>RT (n=43)</td><td>RCT (n=78)</td></tr><tr><td>M/F</td><td>30/13</td><td>60/18</td></tr><tr><td>Mean age</td><td>64.3</td><td>61.8</td></tr><tr><td></td><td></td><td></td></tr><tr><td>T2</td><td>34</td><td>58</td></tr><tr><td>T3-T4</td><td>9</td><td>20</td></tr><tr><td></td><td></td><td></td></tr><tr><td>G2</td><td>12</td><td>23</td></tr><tr><td>G3/4</td><td>31</td><td>55</td></tr><tr><td>Concomitant CIS</td><td></td><td></td></tr><tr><td>Yes</td><td>4</td><td>8</td></tr><tr><td>No</td><td>39</td><td>70</td></tr><tr><td>Hydronephrosis</td><td></td><td></td></tr><tr><td>Yes</td><td>3</td><td>7</td></tr><tr><td>No</td><td>40</td><td>71</td></tr><tr><td>Visibly complete TURB</td><td></td><td></td></tr><tr><td>present</td><td>33</td><td>65</td></tr><tr><td>absent</td><td>10</td><td>13</td></tr></table>	RT: All received neoadjuvant cisplatin-based CT (MCV). EBRT with CT images from a linear accelerator using 4-box field technique. Median dose to pelvis 45Gy and median 65Gy to bladder. Daily fraction 1.8 – 2.0 Gy once daily on 5 consecutive days.	RCT: From 1998 concomitant CT (cisplatin or carboplatin) was given during 1st and 5th week of RT	Median 66 months (range 6-182)	**Overall survival:** 68%; RT 60.4% vs RCT 71.8% (p=.008) **Disease-specific survival:** 74%; RT 62.8% vs RCT 79.4% (p=.003) **Toxicity:** 4 cardiopulmonary events during neoadjuvant CT. 16% thrombocytopenia, 12% cystitis, 12% enteritis. **Acute toxicity (WHO):** Bone marrow: RT 6/43 (13.9%) v RCT 13/78 (16.6%) Bladder: RT 5/43 (9.3%) v 9/78 (11.5%) Intestinal: RT 4/43 (9.3%) v 11/78 (14/1%)	Not reported	
Manger 2006 UK	Retrospective review 1984-1998	229	<table><tr><td></td><td>2 phase N=75</td><td>Single phase N=154</td></tr><tr><td>Median f/up (y)</td><td>3.1</td><td>7.9</td></tr><tr><td>Accelerated fractionation</td><td></td><td></td></tr><tr><td></td><td>16 (21)</td><td>72 (47)</td></tr><tr><td>Male</td><td>64 (85)</td><td>130 (84)</td></tr><tr><td>Female</td><td>11 (15)</td><td>24 (16)</td></tr><tr><td>Technique</td><td></td><td></td></tr><tr><td>Conventional</td><td>66 (88)</td><td>115 (75)</td></tr><tr><td>Conformal</td><td>8 (11)</td><td>26 (17)</td></tr></table>	2 phase RT (n=75): 52Gy to bladder and 12Gy tumour boost in patients with solitary, well-defined tumours No neoadjuvant, concurrent or adjuvant chemo	Conventional single phase whole bladder RT (n=154): Dose modification was carried out for patients receiving accelerated RT such that the total dose was 60.8Gy in 32 fractions in a maximum of 26 days	Median 4.8y (range 0-15)	**Overall survival:** single phase median 2.8y (95% CI, 2.1-3.6), 2 phase group median OS 2.8 y (95% CI 2.2-5.0). HR=0.91 (0.64-1.3) **Toxicity:** grade 3 incontinence risk at 5-yrs= 30% vs 19% for 2-phase treatment, HR 0.41 (0.2-0.81) Two phase treatment resulted in a 2.5x reduction	NHS exec, ICR, Bob champion cancer trust, CRUK	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			Unspecified: 1 (1.3) / 13 (8.4) ≤T2: 41 (55) / 51 (33) T3: 26 (35) / 53 (34) T4: 3 (1.3) / 21 (14) Node -ve: 53 (71) / 103 (67) Grade 3: 53 (71) / 96 (62)				in the risk of toxicity HR 2.46, 1.02-5.91 (univariate analysis) Any overall grade 3-4 late effects 13/53 (24.5%) 2-phase vs 42/96 (43.8%) single phase		
Krause 2011 Germany	Retrospective observational study 1982-2007	473 consecutive patients who underwent TURBT and RCT or RT	366 men/107 females. Mean age 65.3y (range 28-91). pT1: 110 (23) pT2/3: 328 (69) pT4: 34 (7.2) Grade 1: 17 (3.6) Grade 2: 190 (40.2) Grade 3: 266 (56.2) cN0: 414 (87.5) cN+: 29 (6.1) pL0: 284 (60.1) pL1: 189 (39.9) Uni focal: 282 (59.6) Multifocal: 151 (31.9) R0: 142 (30) R1: 152 (32) R2: 160 (33.8)	RCT (n=331): 4 field box technique daily fraction 1.8-2 Gy on 5 consecutive days. Median 53.9Gy to bladder and pelvic LNs. Concurrent CT for 5 days in 1st and 5th wk of RT. 99.4% had platinum-based CT.	RT (n=142): Reasons for RT only therapy were age, high comorbidity and PS.	Median 71.5mo (range 1.9-306m)	**Overall survival:** Median OS for whole cohort =57.5mo. 5-, 10-, 15- OSR = 49%, 30% and 19% RCT median OS =70mo RT = 28.5mo OS correlated with pT stage, LN mets, LVI, achievement of CR, achievement of R0 at initial TUR	Not reported	Patient characteristics not reported separately for RCT and RT
Zietman 2003 USA	Observational study 2001-2002	48 patients from 5 successive bladder sparing protocols using TURBT, CT and RT who were alive and disease-free in 2001	Median age: 68.9 %T3-T4a: 31.9% % Any BCG: 37% % 3+ TURBTs: 23.8% % EBRT bid: 55.3% % women: 25.5%	QoL questionnaire median of 7 years after chemoradiation.	N/a		**Global health function and well-being (SF-36):** Physical functioning overall mean 89. General health perceptions mean 74 **Urinary function:** Urgency 11% men v 25% Female Lacking control:	Financial interest with Eli Lilly Co. And Glaxo Kline Smith	

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>14% m vs. 33% f
Leaking 11% m vs. 45% f
Bowel function: difficulty in control any time in last week 7 (20%) men, 3 (27%) women. Abdominal cramps 6 (17%) men, 0 women</td><td></td><td></td></tr>
<tr><td>Asadauskiene 2010
Lithuania</td><td>Observational study (prospective and retrospective)
2000-2008</td><td>69 pT2-T4a, N0-N1, M0, no previous treatment for any cancer, ECOG PS0-2</td><td>
<table>
<tr><td></td><td>CRT</td><td>RT</td></tr>
<tr><td>Median age</td><td>65</td><td>70.5</td></tr>
<tr><td>Male</td><td>18 (78)</td><td>40 (87)</td></tr>
<tr><td>Female</td><td>5 (21)</td><td>6 (13)</td></tr>
<tr><td>T2</td><td>22 (96)</td><td>44 (96)</td></tr>
<tr><td>T3</td><td>0</td><td>2 (4)</td></tr>
<tr><td>T4</td><td>1 (4.3)</td><td>0</td></tr>
<tr><td colspan="3">Hydronephrosis</td></tr>
<tr><td>No</td><td>14 (61)</td><td>26 (57)</td></tr>
<tr><td>Yes</td><td>9 (39)</td><td>20 (44)</td></tr>
<tr><td>R0</td><td>6 (26)</td><td>9 (20)</td></tr>
<tr><td>R1</td><td>7 (30)</td><td>10 (22)</td></tr>
<tr><td>R2</td><td>10 (44)</td><td>27 (59)</td></tr>
<tr><td colspan="3">Comorbidities</td></tr>
<tr><td>No</td><td>13 (57)</td><td>22 (48)</td></tr>
<tr><td>Yes</td><td>10 (44)</td><td>24 (52)</td></tr>
</table>
</td><td>CRT (n=23): 7 refused RC, 16 comorbidities. Gemcitabine 175-300mg/m^2 once weekly, concomitant with RT for 6 wks. 2 patients 175mg and 21 patients 300mg . 6 patients did not accomplish treatment per protocol</td><td>RT (n=46): Linear accelerator facility used, daily dose 1.8-2.0Gy, total 54-60Gy in 27-30 fractions, 5 days/week over 6 weeks.</td><td>Median 18 mo</td><td>Overall survival: 3-yr OS 38% CRT, 27% RT.</td><td>Not reported</td><td>N stage and grade not reported</td></tr>
<tr><td>Herman 2004
USA</td><td>Observational study
1998-2002</td><td>23 with Gemcitabine and concurrent RT. Initial dose =10mg/m^2 which was increased as tolerated</td><td>100% male, median age 62 (range 46-83). All stage T2, high grade TCC, 7 had associated CIS</td><td>N/a</td><td>N/a</td><td></td><td>Dose-limiting toxicity: 5/22 had at least one DLT
Quality of life (FACT-BL and FACT-G): No differences before, during or after</td><td>Eli Lilly, NCI, NIH</td><td></td></tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							treatment. Patients with more than 20mg/m^2 reported lower QoL scores. FACT-G values were lower for those who experienced a DLT. 11/13 reported increased urine frequency during treatment. Bowel control and erectile function were unchanged from baseline in 71% and 58% of patients.		

5.2.3 Urinary stoma versus bladder reconstruction.

Review question: Is bladder reconstruction or urinary stoma the more effective method of urinary diversion?

Rationale

After removal of the bladder for bladder cancer (cystectomy), drainage of urine has to be re-established. This can be done by using a segment of bowel taken out of circuit from the remaining bowel, re-joining the remaining bowel, and then connecting the tubes draining urine from the kidneys (the ureters) to some configuration of the bowel segment. This can be done either by formation of a urinary stoma (ileal conduit), with urine draining continually into an external bag, or by one or other form of urinary reconstruction, where a pouch is made from bowel, and is connected either to the waterpipe (urethra), as a bladder substitute, or to the skin of the abdominal wall, as a catheterisable reservoir (Mitrofanoff procedure). A bladder substitute allows urine to be held and passed in a more or less normal way, and a catheterisable reservoir is emptied by passage of a catheter around three to four times each day. Neither of these options involve an external bag.

Rehabilitation after this sort of surgery is much quicker with a stoma, and the majority of patients learn very quickly how to empty and change their bag, whereas learning how to use a bladder substitute or a catheterisable reservoir requires much more time and effort on the patient's part, with more follow-up visits.

The price of the more simple and straightforward rehabilitation with a stoma is the need for an external bag continually, and the presence of a piece of bowel at the skin surface, whereas bladder reconstruction leaves only a scar, and no bag. For patients with a bladder substitute, urine is held and passed in a more or less normal way.

The short and long term complication rate is the same with a stoma or a bladder substitute, but catheterisable reservoirs have a re-operation rate of around twice that the other two operations (50%). Bladder reconstruction requires reasonable kidney function (to deal with the effect of absorption of acid substances by the pouch), normal bowel function (no inflammatory bowel disease), and motivation and adequate mental capacity.

There is no evidence that either health-related outcomes or health-related quality of life differ significantly with any of these forms of urinary diversion, and the decision for patients is based on whether they are offered choice, and then which form of diversion fits with their own priorities. This decision is made, ideally, after discussion with a specialist urologist, and with a specialist nurse and with patients who have had this kind of surgery. This is probably not routine in cancer centres in England and Wales.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients having cystectomy for bladder cancer	Bladder reconstruction/replacement Ileal conduit Continent diversion	Each other	• Treatment-related morbidity • Treatment-related mortality • Adverse events • Patient satisfaction • Health-related quality of life, inc patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

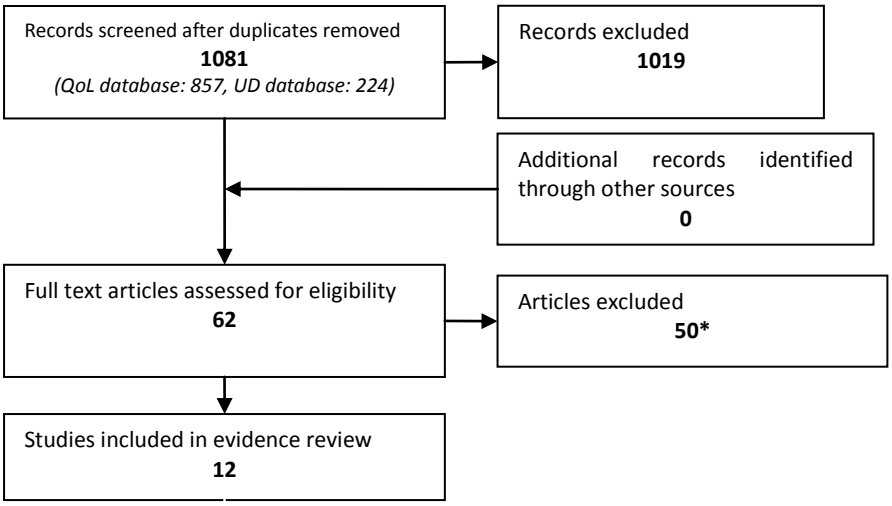
The information specialist (EH) did the first screen of the literature search results. One reviewer (LB) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. An existing systematic review was identified for this topic and, after correspondence with the GDG, a decision was made not to update the review but to select randomised trials published since 2006, as any further observational studies were not likely to be useful in answering the review question. Comparative studies reporting quality of life outcomes were also selected.

Data synthesis

RESULTS

Result of the literature searches

Figure 70. Study flow diagram



Note. *The Skinner and Skinner (2009) article was excluded without reading the full text article as it was difficult to access. A comparison was made to a latter included Skinner paper (2012) which used the same comparisons and a decision was made to exclude the 2009 article on the basis that it was assessing type of orthotopic surgical techniques (Skinner, E. C. and Skinner, D. G. "Does reflux in orthotopic diversion matter? A randomized prospective comparison of the Studer and T-pouch ileal neobladders." World Journal of Urology 27.1 (2009): 51-55.).

Study quality and results

Evidence was identified from one systematic review of 557 studies and ten further observational studies reporting quality of life. No randomised trials published since the existing systematic review were identified. Evidence is summarised in Tables 117-118.

Evidence statements

Low quality evidence from one systematic review of 557 studies (46,921 patients) (Somani *et al.*, 2009) assessing adverse events associated with type of urinary diversion indicates uncertainty over the most effective surgical option. Whilst the percentage of patients reporting some adverse events varied depending on type of urinary diversion (in some instances varied considerably according to study design) none of the differences presented reached statistical significance (unclear how this was assessed as no statistical analyses are presented in the article). Somani *et al.* (2009) proposed that the lack of statistical significance does not provide evidence of lack of equivalence or evidence of lack of superiority of one intervention over the other but could be attributable to better patient selection for type of urinary diversion (e.g. younger and fitter patients undergoing bladder replacement).

Prospective studies favoured ileal conduit for fewer operative complications compared to the continent diversions (6.1% versus 25.7%, respectively). However, postoperative morbidity favoured the continent diversions compared to ileal conduit (11.4% versus 27%, respectively).

More upper tract UTIs were reported in the ileal conduit patients compared to the continent diversions patients (26.5% versus 8.1%, respectively). Further, Ileal conduit patients reported more metabolic alkalosis (23.8% versus 2.7%), higher rates of bone disease (70.4% of ileal conduit patients versus 19.8% of continent patients), and increased problems with odour (67.6% versus 28.6%) compared to continent diversion patients.

A higher incidence of urinary stones were reported in the continent diversion patients (14.1% [prospective studies] and 15.9% [retrospective studies]) compared to the ileal conduit patients versus (5.2% [retrospective studies]). In addition, continent diversion patients reported higher rates of faecal incontinence (10.8% of continent patients versus 0% of ileal conduit patients) and flatus leakage (28.6% of continent patients versus 5% of ileal conduit patients) compared to the ileal conduit patients.

There was no comparative data for lower tract UTIs or clean intermittent self-catheterisation but in both adverse events over 20% of continent patients reported these issues (prospective data: 23.8% lower tract UTIs; 28.3% clean intermittent self-catheterisation). No comparative for prospective studies was found comparing types of diversion for metabolic acidosis, with 39.4% of continent diversion patients reporting this event. However, comparative data for retrospective studies reported a higher frequency of the adverse event in the continent patients compared to ileal conduit patients (25.0% versus 3.1%, respectively).

Health related quality of life and patient satisfaction was reported by one low quality systematic review of 46 studies (4,186 patients) and ten very low quality observational studies (725 patients). The majority of the 56 studies reviewed reported that patients had good HRQoL/global satisfaction (13/56 studies: 23%) or that there were no statistically significant differences between the groups compared on HRQoL/satisfaction (19/56 studies: 34%). Of the remaining studies 20/56 (36%) reported that there were differences between the groups compared. The systematic review provided minimal information on these statistically differences, and implied that the pooled results reveal inconsistent findings across the different types of urinary diversions. For example, three studies reported poorer outcomes for patients receiving an orthotopic bladder replacement compared to patients receiving ileal conduit diversions or control participants (e.g. more urinary leakage; reduced physical health, reduced emotional problems and higher bodily pain; low body image), whereas three other studies reported better outcomes for these orthotopic bladder patients (e.g. HRQoL better in all domains; higher physical functioning). Inconsistent results across the different types of urinary diversions were also found in the ten very low quality observational studies. In addition, the majority of these significant differences were in one or two sub-scale analyses and did not reflect global HRQoL differences between the compared groups.

Four studies (two retrospective, two prospective) out of the 46 studies included in the low quality systematic review assessed the impact of psychological interventions (e.g. pre-operative counselling [no additional information provided on what the “interventions” were, how they were measured]) on HRQoL and patient satisfaction outcomes. The two retrospective studies reported an increase in satisfaction scores post-surgery following pre-operative counselling.

Table 117. GRADE evidence profile: Urinary diversions and adverse events

PLEASE NOTE: The Continent diversions category was computed by summing any data reported for each adverse event from the following groups of patients in the Somani (2009) review article: continent diversion patients (*continent cutaneous diversion, ureterosigmoidostomy and the newer variants of ureterosigmoidostomy*), bladder reconstruction patients (*native bladder remains in situ and is surgically manipulated to improve its function*) and bladder replacement patients (n*ative bladder was removed completely and a new reservoir was created, positioned where the native bladder used to be and connected to the native urethra, therefore, allowing patients to void in the natural way*).

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
Postoperative morbidity - Ileal conduit Prospective											
13[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	317/1175 (27%)	-	-	-	LOW
Postoperative morbidity - Continent diversions Prospective											
13[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	87/766 (11.4%)	-	-	-	LOW
Postoperative morbidity - Ileal conduit Retrospective											
134[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	555/2317 (24%)	-	-	-	LOW
Postoperative morbidity - Continent diversions Retrospective											
134[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	1663/9294 (17.9%)	-	-	-	LOW
Postoperative mortality - Ileal conduit Prospective											
15[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	29/1159 (2.5%)	-	-	-	LOW
Postoperative mortality - Continent diversions Prospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
15[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	55/2175 (2.5%)	-	-	-	LOW
Postoperative mortality - Ileal conduit Retrospective											
106[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	82/1911 (4.3%)	-	-	-	LOW
Postoperative mortality - Continent diversions Retrospective											
106[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	361/8628 (4.2%)	-	-	-	LOW
Operative complications - Ileal conduit Prospective											
2[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	8/132 (6.1%)	-	-	-	LOW
Operative complications - Continent diversions Prospective											
2[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	9/35 (25.7%)	-	-	-	LOW
Operative complications - Ileal conduit Retrospective											
30[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	47/365 (12.9%)	-	-	-	LOW
Operative complications - Continent diversions Retrospective											
30[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	174/1633 (10.7%)	-	-	-	LOW
Need for reoperation - Ileal conduit Prospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
17[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	3/116 (2.6%)	-	-	-	LOW
Need for reoperation - Continent diversions Prospective											
17[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	141/13611 (1%)	-	-	-	LOW
Need for reoperation - Ileal conduit Retrospective											
190[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	270/1673 (16.1%)	-	-	-	LOW
Need for reoperation - Continent diversions Retrospective											
190[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	1316/10895 (12.1%)	-	-	-	LOW
Bowel anastomotic leakage - Continent diversions Prospective											
1	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	1/33 (3%)	-	-	-	LOW
Bowel anastomotic leakage - Ileal conduit Retrospective											
39[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	19/724 (2.6%)	-	-	-	LOW
Bowel anastomotic leakage - Continent diversions Retrospective											
39[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	95/3069 (3.1%)	-	-	-	LOW
Bladder/ureteroenteric anastomtic leakage - Continent diversions Prospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
3	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	15/309 (4.9%)	-	-	-	LOW
Bladder/ureteroenteric anastomtic leakage - Ileal conduit Retrospective											
45[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	37/999 (3.7%)	-	-	-	LOW
Bladder/ureteroenteric anastomtic leakage - Continent diversions Retrospective											
45[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	202/3719 (5.4%)	-	-	-	LOW
Upper tract Urinary Tract Infection - Ileal conduit Prospective											
14[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	13/49 (26.5%)	-	-	-	LOW
Upper tract Urinary Tract Infection - Continent diversions Prospective											
14[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	55/682 (8.1%)	-	-	-	LOW
Upper tract Urinary Tract Infection - Ileal conduit Retrospective											
101[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	167/3080 (5.4%)	-	-	-	LOW
Upper tract Urinary Tract Infection - Continent diversions Retrospective											
101[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	454/6396 (7.1%)	-	-	-	LOW
Lower tract Urinary Tract Infection - Continent diversions Prospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
7	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	284/1192 (23.8%)	-	-	-	LOW
Lower tract Urinary Tract Infection - Continent diversions Retrospective											
70	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	368/3070 (12%)	-	-	-	LOW
Clean intermittent self-catheterisation - Continent diversions Prospective											
9	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	230/814 (28.3%)	-	-	-	LOW
Clean intermittent self-catheterisation - Continent diversions Retrospective											
83	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	1458/4644 (31.4%)	-	-	-	LOW
Catheter blockage - Continent diversions Prospective											
2	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	9/136 (6.6%)	-	-	-	LOW
Catheter blockage - Continent diversions Retrospective											
15	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	64/1566 (4.1%)	-	-	-	LOW
Diarrhea - Ileal conduit Prospective											
3[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	10/76 (13.2%)	-	-	-	LOW
Diarrhea - Continent diversions Prospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
3[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	17/151 (11.3%)	-	-	-	LOW
Diarrhea - Ileal conduit Retrospective											
36[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	9/210 (4.3%)	-	-	-	LOW
Diarrhea - Continent diversions Retrospective											
36[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	203/2592 (7.8%)	-	-	-	LOW
Stress incontinence - Continent diversions Prospective											
15	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	29/958 (3%)	-	-	-	LOW
Stress incontinence - Ileal conduit Retrospective											
54[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	1/20 (5%)	-	-	-	LOW
Stress incontinence - Continent diversions Retrospective											
54[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	231/3330 (6.9%)	-	-	-	LOW
Odor - Ileal conduit Prospective											
2[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	23/34 (67.6%)	-	-	-	LOW
Odor - Continent diversions Prospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
2[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	6/21 (28.6%)	-	-	-	LOW
Odor - Ileal conduit Retrospective											
3[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	34/58 (58.6%)	-	-	-	LOW
Odor - Continent diversions Retrospective											
3[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	7/115 (6.1%)	-	-	-	LOW
Stomal stenosis - Continent diversions {Prospective											
2	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	9/81 (11.1%)	-	-	-	LOW
Stomal stenosis - Ileal conduit Retrospective											
88[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	81/1860 (4.4%)	-	-	-	LOW
Stomal stenosis - Continent diversions Retrospective											
88[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	556/5023 (11.1%)	-	-	-	LOW
Hernia - Ileal conduit Retrospective											
35[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	45/1227 (3.7%)	-	-	-	LOW
Hernia - Continent diversions Retrospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
35[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	65/2746 (2.4%)	-	-	-	LOW
Faecal urgency - Ileal conduit Retrospective											
5[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	0/29 (0%)	-	-	-	LOW
Faecal urgency - Continent diversions Retrospective											
5[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	15/347 (4.3%)	-	-	-	LOW
Faecal incontinence - Ileal conduit Retrospective											
5[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	0/29 (0%)	-	-	-	LOW
Faecal urgency - Continent diversions Retrospective											
5[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	32/295 (10.8%)	-	-	-	LOW
Flatus leakage - Ileal conduit Retrospective											
2[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	5/100 (5%)	-	-	-	LOW
Flatus leakage - Continent diversions Retrospective											
2[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	8/28 (28.6%)	-	-	-	LOW
Constipation - Ileal conduit Retrospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
7[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	9/122 (7.4%)	-	-	-	LOW
Constipation - Continent diversions Retrospective											
7[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	25/181 (13.8%)	-	-	-	LOW
Upper tract dilation - Continent diversions Prospective											
14	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	163/1059 (15.4%)	-	-	-	LOW
Upper tract dilation - Ileal conduit Retrospective											
119[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	192/1482 (13%)	-	-	-	LOW
Upper tract dilation - Continent diversions Retrospective											
119[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	756/4578 (16.5%)	-	-	-	LOW
Uterointestinal stenosis - Ileal conduit Prospective											
19[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	14/126 (11.1%)	-	-	-	LOW
Uterointestinal stenosis - Continent diversions Prospective											
19[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	84/1658 (5.1%)	-	-	-	LOW
Uterointestinal stenosis - Ileal conduit Retrospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
134[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	131/1625 (8.1%)	-	-	-	LOW
Uterointestinal stenosis - Continent diversions Retrospective											
134[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	708/6124 (11.6%)	-	-	-	LOW
Renal failure - Continent diversions Prospective											
8	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	32/239 (13.4%)	-	-	-	LOW
Renal failure - Ileal conduit Retrospective											
91[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	76/1744 (4.4%)	-	-	-	LOW
Renal failure - Continent diversions Retrospective											
91[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	297/4006 (7.4%)	-	-	-	LOW
Metabolic acidosis - Continent diversions Prospective											
9	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	404/1025 (39.4%)	-	-	-	LOW
Metabolic acidosis - Ileal conduit Retrospective											
117[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	18/585 (3.1%)	-	-	-	LOW
Metabolic acidosis - Continent diversions Retrospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
117[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	1008/4029 (25%)	-	-	-	LOW
Metabolic alkalosis - Ileal conduit Retrospective											
16[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	24/101 (23.8%)	-	-	-	LOW
Metabolic alkalosis - Continent diversions Retrospective											
16[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	12/449 (2.7%)	-	-	-	LOW
Urinary stones - Continent diversions Prospective											
10	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	194/1379 (14.1%)	-	-	-	LOW
Urinary stones - Ileal conduit Retrospective											
138[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	90/1720 (5.2%)	-	-	-	LOW
Urinary stones - Continent diversions Retrospective											
138[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	953/6005 (15.9%)	-	-	-	LOW
Vitamin B12 deficiency - Continent diversions Prospective											
2	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	2/138 (1.4%)	-	-	-	LOW
Vitamin B12 deficiency - Ileal conduit Retrospective											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
29[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	9/157 (5.7%)	-	-	-	LOW
Vitamin B12 deficiency - Continent diversions Retrospective											
29[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	76/694 (11%)	-	-	-	LOW
Bone disease - Ileal conduit Retrospective											
8[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	19/27 (70.4%)	-	-	-	LOW
Bone disease - Continent diversions Retrospective											
8[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	52/263 (19.8%)	-	-	-	LOW

[1] Data from systematic review by Somani et al. (2009). Number of studies is provided according to prospective/retrospective and not broken down by urinary diversion. For each adverse event that is from prospective data the number of studies will not differ between ileal conduit and continent diversions. For each adverse event that is from retrospective data the number of studies will not differ between ileal conduit and continent diversions.

[2] Study design unknown for each adverse event as authors categorise studies into prospective and retrospective with no further break down of design.

[3] Author's assessed study quality according to a checklist (unclear whether checklist developed by the authors). Score total = 27. Author's only provided average total score according to pooled studies (e.g., retrospective versus prospective) and not according to each adverse event so no information can be assessed on quality of study design per adverse event outcome.

[4] For the Ileal conduit prospective studies the study quality mean score (assessed by the author's quality checklist) was 9.75/27.

[5] For the Continent diversions prospective studies the study quality mean score (assessed by the author's quality checklist) was 9.22/27.

[6] For the Ileal conduit retrospective studies the study quality mean score (assessed by the author's quality checklist) was 7/27.

[7] For the Continent diversions retrospective studies the study quality mean score (assessed by the author's quality checklist) was 7.4/27.

Table 118. GRADE evidence profile: Urinary diversions and Health Related Quality of Life (HRQoL) and Patient Satisfaction

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Effect		
									Relative (95% CI)	Absolute	
HRQOL and Patient Satisfaction Systematic Review (Somani et al. 2010)											
46[1]	observational studies	no serious limitations[2]	no serious inconsistency[2]	no serious indirectness[2]	no serious imprecision[2]	none[2]	0/4186 (0%)	-	-	-	LOW
HRQOL and Patient Satisfaction											
10	observational studies	no serious limitations	no serious inconsistency	serious[3]	no serious imprecision	none	0/725 (0%)	-	-	-	VERY LOW

[1] Data from systematic review by Somani et al. (2010).

[2] No assessment of study quality presented in article. Paragraph in discussion summarising quality, mentioning some limitations of all included studies (e.g. selection bias, non-randomised, no baseline measurement).

[3] Variation in scales used across included studies (Sherwani, 2009 used a self-designed non-validated scales) and in the interpretation of the validated scales used (e.g. sub-scale totals and total scores differed across studies using the same scales). Variation in the methods used to collect the data with two studies (Gacci, 2013; Sherwani, 2009) being unclear on how data was obtained from the participants (e.g. during consultation, self-assessed). In addition, almost half of the included articles failed to explain how to interpret the numbers provided in the results regarding the QoL scales (e.g. high or low quality of life).

References to included studies

Asgari, MA et al. Quality of life after radical cystectomy for bladder cancer in men with an ileal conduit or continent urinary diversion: A comparative study. Urology annals 2013; 5(3): 190-196.

Asgari, MA et al. Sexual Function after Non-Nerve-Sparing Radical Cystoprostatectomy: A Comparison between Ileal Conduit Urinary Diversion and Orthotopic Ileal Neobladder Substitution. International Braz J Urol 2013; 39(4): 474-483.

Erber, B et al. Morbidity and Quality of Life in Bladder Cancer Patients following Cystectomy and Urinary Diversion: A Single-Institution Comparison of Ileal Conduit versus Orthotopic Neobladder. ISRN Urology 2012; 342796.

Gacci, M et al. Quality of life in women undergoing urinary diversion for bladder cancer: results of a multicenter study among long-term disease-free survivors. Health & Quality of Life Outcomes 2013; 11: 43.

Harano, M et al. A pilot study of the assessment of the quality of life, functional results, and complications in patients with an ileal neobladder for invasive bladder cancer. International Journal of Urology 2007; 14(2): 112-117.

Metcalfe, M et al. Association between urinary diversion and quality of life after radical cystectomy. Canadian Journal of Urology 2013; 20(1): 6626-6631.

Sherwani, AY et al. Comparative study of various forms of urinary diversion after radical cystectomy in muscle invasive carcinoma urinary bladder. International Journal of Health Sciences 2009; 3(1): 3-11.

Shim, B et al. Body image following radical cystectomy and ileal neobladder or conduit in korean patients. Korean Journal of Urology 2014; 55(3): 161-166.

Singh, V et al. Prospective comparison of quality-of-life outcomes between ileal conduit urinary diversion and orthotopic neobladder reconstruction after radical cystectomy: a statistical model. BJU International 2014; 113(5): 726-732.

Somani, BK et al. How Close Are We to Knowing Whether Orthotopic Bladder Replacement Surgery Is the New Gold Standard?-Evidence From a Systematic Review Update. Urology 2009; 74(6): 1331-1339.

Somani, BK et al. Quality of Life With Urinary Diversion. European Urology 2010, Supplements 9: 763-771.

Vakalopoulos, I et al. Does intubated uretero-ureterocutaneostomy provide better health-related quality of life than orthotopic neobladder in patients after radical cystectomy for invasive bladder cancer? International Urology and Nephrology 2011; 43(3): 743-748.

References to excluded studies (with reasons for exclusion)

Study	Reason for exclusion
1. Weizer, A. et al. "Results from A Randomized Controlled Study of Prostate Capsule Sparing (Pcs) Versus Nerve Sparing (Ns) Cystectomy and Orthotopic Neobladder for Urothelial Cancer." Journal of Urology 187.4 (2012): E570-E571.	**Cystectomy surgical techniques** *(prostate capsule sparing versus nerve sparing)* – Conference abstract.
2. Harano, M. "Assessment of the quality of life, complications, oncological outcome and change in renal function in patients with ileal neobladder due to invasive bladder cancer." Nishinihon Journal of Urology 68.10 (2006): 459-465.	**Foreign language** – Japanese – Retrospective – ONB versus cutaneous diversion – N=41 – Could be same sample as used in the Harano et al. 2007 paper.
3. Hugonnet, C. L. et al. "[Long-term urodynamic and clinical follow-up in 70 patients with ileal bladder replacement combined with an antireflux mechanism or an afferent tubular segment]." Progrès.en.urologie.: journal de l'Association.française.d'urologie.et de la Société.française.d'urologie. 7.6 (1997): 960-966.	**Foreign language** – French – Reflux prevention techniques in orthotopic bladder reconstruction.
4. Mottet, N. "Quality of life after cystectomy: French national survey conducted by the Association francaise d'urologie (AFU), the Federation des stomises de France (FSF) and the Association francaise des enterostomatherapeutes (AFET) in patients with ileal conduit urinary diversion or orthotopic neobladder." Progres En Urologie 18.5 (2008): 292-298.	**Foreign language** – French – Retrospective – N=877 – IC versus ONB – Satisfaction scores and disability scores
5. Hautmann, R. E. et al. "Urinary diversion." Urology 69.(2007): 17-49.	**Literature review** – <2007 – International group from WHO and SIU – % UD in >7000 patients – No info on search strategy – No grading of evidence – QoL section
6. Kassouf, W. et al. "A critical analysis of orthotopic bladder substitutes in adult patients with bladder cancer: is there a perfect solution?. [Review]." European Urology 58.3 (2010): 374-383.	**Literature review** – 1990-2010 – Orthotopic bladder substitution – Mainly clinical practice used to suggest guidelines – QoL section
7. Stenzl, A. et al. "Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. [Review]." European Urology 59.6 (2011): 1009-1018.	**Literature review** – >2008 – EAU guidelines – Expert consensus – Grading of literature and recommendations presented
8. Wright, J. L. and Porter, M. P. "Quality-of-life assessment in patients with bladder cancer. [Review] [42 refs]." Nature Clinical Practice Urology 4.3 (2007): 147-154.	**Literature Review** – ≤2004
9. Hautmann, R. E. et al. "ICUD-EAU International Consultation on Bladder Cancer 2012: Urinary diversion. [Review]." European Urology 63.1 (2013): 67-80.	**Narrative review** – <2012
10. Colombo, R. and Naspro, R. "Ileal Conduit as the Standard for Urinary Diversion After Radical Cystectomy for Bladder Cancer." European Urology Supplements 9.10 (2010): 736-744.	**Narrative review** – <2010
11. Daneshmand, S. and Bartsch, G. "Improving selection of appropriate urinary diversion following radical cystectomy for bladder cancer. [Review]." Expert Review of Anticancer Therapy 11.6 (2011): 941-948.	**Narrative review** – <2007
12. Hautmann, R. E., Hautmann, S. H., and Hautmann, O. "Complications associated with urinary diversion." Nature Reviews Urology 8.12 (2011): 667-677.	**Narrative review** – <2011
13. Park, J. and Ahn, H. "Radical cystectomy and orthotopic bladder substitution using ileum." Korean Journal of Urology 52.4 (2011): 233-240.	**Narrative review** – <2011
14. Shih, C. and Porter, M. P. "Health-related quality of life after cystectomy and urinary diversion for bladder cancer." Advances in Urology 2011.(2011):	**Narrative review** – <2011

Study	Reason for exclusion
715892-	
15. Jiansong, W. "Bladder neoplasms, orthotropic, urinary diversion, the quality of life, SF-36 general health survey." International Journal of Urology Conference.var.pagings (2012): 433-	**Orthotopic neobladder versus non-orthotopic urinary diversion** – Retrospective – No significance data presented. – Conference abstract.
16. Davidsson, T., Hedlund, H., and Månsson, W. "Detubularized right colonic reservoir with intussuscepted ileal nipple valve or stapled ileal ("Lundiana") outlet. Clinical and urodynamic results in a prospective randomized study." World Journal of Urology 14.2 (1996): 78-84.	**Orthotopic urinary diversion surgical techniques** *(ileal nipple valve versus stapled ileal)*
17. Chen, Z. et al. "Better compliance contributes to better nocturnal continence with orthotopic ileal neobladder than ileocolonic neobladder after radical cystectomy for bladder cancer." Urology 73.4 (2009): 838-843.	**Orthotopic urinary diversion surgical techniques** *(ileal versus colon)*
18. Khafagy, M., Shaheed, F. A., and Moneim, T. A. "Ileocaecal vs ileal neobladder after radical cystectomy in patients with bladder cancer: a comparative study." BJU.international. 97.4 (2006): 799-804.	**Orthotopic urinary diversion surgical techniques** *(ileocaecal versus ileal)*
19. Miyake, H. "Orthotopic neobladder reconstruction following radical cystectomy in Japanese women: Comparative study between sigmoid and ileal neobladders." Journal of Urology Conference.var.pagings (2010): 4-	**Orthotopic urinary diversion surgical techniques** *(sigmoid versus ileal neobladder)*
20. Miyake, H. et al. "Health related quality of life after radical cystectomy: comparative study between orthotopic sigmoid versus ileal neobladders." European Journal of Surgical Oncology 38.11 (2012): 1089-1094.	**Orthotopic urinary diversion surgical techniques** *(sigmoid versus ileal neobladder)*
21. Miyake, H. et al. "Orthotopic bladder substitution following radical cystectomy in women: comparative study between sigmoid and ileal neobladders." Urologic Oncology 30.1 (2012): 38-43.	**Orthotopic urinary diversion surgical techniques** *(sigmoid versus ileal neobladder)* – Conference abstract.
22. Ahmadi, H. et al. "Urinary functional outcome following radical cystoprostatectomy and ileal neobladder reconstruction in male patients." Journal of Urology 189.5 (2013): 1782-1788.	**Orthotopic urinary diversion surgical techniques** *(Studer pouch versus T-pouch)*
23. Fairey, A. et al. "Effect of Studer Pouch Versus T-Pouch Orthotopic Ileal Bladder Substitution on Late Complications and Surgical Re-Intervention in Bladder Cancer Patients Undergoing Radical Cystectomy: Secondary Analyses from the Usc-Star Randomized Trial." Journal of Urology 189.4 (2013): E579-E580.	**Orthotopic urinary diversion surgical techniques** *(Studer pouch versus T-pouch)*
24. Skinner, E. C. and Skinner, D. G. "Does reflux in orthotopic diversion matter? A randomized prospective comparison of the Studer and T-pouch ileal neobladders." World Journal of Urology 27.1 (2009): 51-55.	**Orthotopic urinary diversion surgical techniques** *(Studer pouch versus T-pouch)* Full paper was not received as hard to access. Search was cancelled and the reference made to Skinner et al. 2012 paper which was excluded due to an RCT on Orthotopic urinary diversion surgical techniques (Studer pouch versus T-pouch). Abstract compares the same groups.
25. Skinner, E. et al. "Randomized Trial of Studer Pouch Versus T-Pouch Orthotopic Urinary Diversion in Bladder Cancer Patients: Interim Analysis of Effect on Renal Function at 3 Years." Journal of Urology 187.4 (2012): E468-E469.	**Orthotopic urinary diversion surgical techniques** *(Studer pouch versus T-pouch)* – Conference abstract.
26. Osman, Y. et al. "Comparison between a serous-lined extramural tunnel and T-limb ileal procedure as an antireflux technique in orthotopic ileal substitutes: a prospective randomized trial." BJU.international. 104.10 (2009): 1518-1521.	**Reflux prevention techniques in orthotopic bladder reconstruction.**
27. Osman, Y. et al. "Long-term results of a prospective randomized study comparing two different antireflux techniques in orthotopic bladder substitution." European.urology 45.1 (2004): 82-86.	**Reflux prevention techniques in orthotopic bladder reconstruction.**
28. Shaaban, A. A. et al. "Urethral controlled bladder substitution: a comparison between the intussuscepted nipple valve and the technique of Le Duc as antireflux procedures." The.Journal of urology 148.4 (1992): 1156-1161.	**Reflux prevention techniques in orthotopic bladder reconstruction.**
29. Studer, U. E. et al. "Ileal bladder substitute: antireflux nipple or afferent tubular segment?" European.urology 20.4 (1991): 315-326.	**Reflux prevention techniques in orthotopic bladder reconstruction.**
30. Xu, A. et al. "Comparison of seromuscular tunnel and split-cuff nipple	**Reflux prevention techniques in orthotopic bladder reconstruction.**

Study	Reason for exclusion
antireflux ureteroenteral anastomosis techniques in orthotopic taenia myectomy sigmoid neobladder: a prospective, randomized study." Urology 81.3 (2013): 669-674.	
31. Kristjánsson, A., Wallin, L., and Månsson, W. "Renal function up to 16 years after conduit (refluxing or anti-reflux anastomosis) or continent urinary diversion. 1. Glomerular filtration rate and patency of uretero-intestinal anastomosis." British.journal of urology 76.5 (1995): 539-545.	**Sample includes > Bladder cancer** – Outcome(s): renal function at 10 years. – 4/56 patients did not have bladder cancer.
32. Cody, J. D. et al. "Urinary diversion and bladder reconstruction/replacement using intestinal segments for intractable incontinence or following cystectomy." Cochrane.Database.of Systematic.Reviews. 2 (2012):	**Sample includes > Bladder cancer** Systematic review which found one RCT comparing continent versus conduit diversion but the sample included >bladder cancer patients *(Kristjansson et al. 1995)*.
33. Gemmill, R. et al. "Going with the flow: quality-of-life outcomes of cancer survivors with urinary diversion." Journal of Wound, Ostomy, & Continence Nursing 37.1 (2010): 65-72.	**Sample includes > Bladder cancer** – Prostate, cervical, bladder plus other organs, missing). – Retrospective – COHHRQOL-O – N=307 – No data on type of UD only incontinent versus continent
34. Forner, D. M. and Lampe, B. "Ileal Conduit and Continent Ileocecal Pouch for Patients Undergoing Pelvic Exenteration Comparison of Complications and Quality of Life." International Journal of Gynecological Cancer 21.2 (2011): 403-408.	**Sample: patients with gynecologic cancer** – QoL in patients receiving ileal conduit or continent ilieocecal pouch
35. Autorino, R. et al. "Health related quality of life after radical cystectomy: comparison of ileal conduit to continent orthotopic neobladder." European Journal of Surgical Oncology 35.8 (2009): 858-864.	**Study included in Somani 2010 systematic review**
36. Frich, P. S., Kvestad, C. A., and Angelsen, A. "Outcome and quality of life in patients operated on with radical cystectomy and three different urinary diversion techniques." Scandinavian Journal of Urology and Nephrology 43.1 (2009): 37-41.	**Study included in Somani 2010 systematic review**
37. Gilbert, S. M. et al. "Measuring health-related quality of life outcomes in bladder cancer patients using the Bladder Cancer Index (BCI)." Cancer 109.9 (2007): 1756-1762.	**Study included in Somani 2010 systematic review**
38. Hedgepeth, R. C. et al. "Body Image and Bladder Cancer Specific Quality of Life in Patients With Ileal Conduit and Neobladder Urinary Diversions." Urology 76.3 (2010): 671-675.	**Study included in Somani 2010 systematic review**
39. Kikuchi, E. et al. "Assessment of long-term quality of life using the FACT-BL questionnaire in patients with an ileal conduit, continent reservoir, or orthotopic neobladder." Japanese Journal of Clinical Oncology 36.11 (2006): 712-716.	**Study included in Somani 2010 systematic review**
40. Philip, J. et al. "Orthotopic neobladder versus ileal conduit urinary diversion after cystectomy--a quality-of-life based comparison." Annals of the Royal College of Surgeons of England 91.7 (2009): 565-569.	**Study included in Somani 2010 systematic review**
41. Protogerou, V. et al. "Modified S-pouch neobladder vs ileal conduit and a matched control population: a quality-of-life survey." BJU International. 94.3 (2004): 350-354.	**Study included in Somani 2010 systematic review**
42. Sogni, F. et al. "Morbidity and quality of life in elderly patients receiving ileal conduit or orthotopic neobladder after radical cystectomy for invasive bladder cancer." Urology 71.5 (2008): 919-923.	**Study included in Somani 2010 systematic review**
43. Somani, B. "Is the quality of life (QOL) and body image with continent diversion or neobladder better than ileal conduit diversion? Evidence from a systematic review." European Urology, Supplements Conference.var.pagings (2009): 4-	**Superseded by Somani 2010 systematic review full paper.** – Abstract for conference
44. Somani, B. K. "Is the quality of life (QOL) and body image with continent diversion or neobladder better than ileal conduit diversion? Evidence from a systematic review." Journal of Urology Conference.AUA (2009): var-	**Superseded by Somani 2010 systematic review full paper.** – Abstract for conference
45. Anderson, C. B. et al. "Psychometric characteristics of a condition-specific, health-related quality-of-life survey: the FACT-Vanderbilt Cystectomy Index." Urology 80.1 (2012): 77-83.	**Validity study assessing the FACT-VCI** – Authors include three samples to assess the scale validity – One sample includes pre and post

Study	Reason for exclusion
	operative HRQOL – However, no information on specific breakdown per UD for each sample making data and results difficult to interpret and extract.
46. De Nunzio, C et al. Analysis of radical cystectomy and urinary diversion complications with the Clavien classification system in an Italian real life cohort. Ejso 2013; 39(7): 792-798.	- Not relevant to PICO
47. Gilbert, SM et al. Downstream Complications Following Urinary Diversion. Journal of Urology 2013; 190(3): 916-922.	- Not QoL outcomes
48. Yang, M et al. Impact of invasive bladder cancer and orthotopic urinary diversion on general health-related quality of life: An SF-36 survey. Mol.Clin.Oncol. 2013; 1(4): 758-762.	- Comparison not relevant to PICO
49. Ahmed, K et al. Analysis of Intracorporeal Compared with Extracorporeal Urinary Diversion After Robot-assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium. European Urology 2014; 65(2): 340-347.	- Comparison not relevant to PICO
50. Lee, RK et al. Urinary diversion after radical cystectomy for bladder cancer: options, patient selection, and outcomes. BJU International 2014; 113(1): 11-23.	- Expert review

Evidence tables

Somani, BK et al. "How Close Are We to Knowing Whether Orthotopic Bladder Replacement Surgery Is the New Gold Standard?-Evidence From a Systematic Review Update." Urology 74.6 (2009): 1331-1339.

Objective of review: Consider the clinical effectiveness and risk profile of the different types of surgeries using transposed intestinal segments.

Pub year: 2009

Search Period	Jan 1990 – Jan 2007
Abstracts reviewed	5,651
Studies included	557
Study designs	9: RCT 25: Prospective cohorts 20: Prospective comparative 75: Retrospective comparative 428: Retrospective case series
Participants of included studies	46,921
Countries of included studies	No information provided.
Funding source	No information provided.

Review Methods

Inclusion criteria: All relevant studies reporting on surgery involving intestinal segments transposed into the urinary tract. Articles published in English language reporting at least 10 patients and a mean follow-up of at least 1 year.

Search engines: MEDLINE, PUBMED, EMBASE, CINAHL, Cochrane Library.

Data extract and study appraisal: Articles were categorized into study design and two observers independently performed data extract and in the event of disagreement a consensus was achieved after assessment by a third party.

Quality

Results

Quality assessment: As shown in Table I, the quality of reporting was poor as were the scores reflecting study design.

Table I. Literature quality according to study design and UD type, as assessed by predetermined checklist.

		A. Ileal conduit		B. Continent diversion		C. Bladder reconstruction		D. Bladder replacement	
		N = 8969		N = 13892		N = 7324		N = 16662	
Design	N studies	Median score (range)	N patients	Median score (range)	N patients	Median score (range)	N patients	Median score (range)	N patients
RCT	9	13 (5-17)	187	13 (5-17)	136	13 (5-17)	43	5 (5-15)	250
Prospective									
Cohorts	25	10 (7-12)	1141	10 (7-13)	486	10 (7-12)	190	11 (7-12)	935
Concurrent control	19	9 (2-14)	906	8 (2-14)	2733	5 (2-14)	1342	8 (2-14)	1726
Historical control	1	7 (2-12)	48	-	-	-	-	-	-
Retrospective									
Concurrent control	65	7 (2-13)	2311	7 (2-13)	4035	7 (2-12)	1081	9 (2-13)	4352
Historical control	10	9 (9-13)	585	11 (6-13)	368	10 (6-13)	145	9 (6-13)	608
Retrospective case series									
Multiple unit large	6	4 (3-10)	426	10 (3-10)	106	-	-	4 (1-6)	242
Large	222	8 (0-12)	3162	7 (0-12)	4566	7 (0-12)	3811	7 (0-13)	6829
Small	200	7 (2-12)	555	8 (1-12)	1278	8 (2-12)	959	7 (2-12)	1900

Note. Retrospective case studies with less and more than 100 patients were categorised as small and larger, respectively. Definition of diversions taken from Nabi et al. (2005) for which the Somani (2009) article is an update. Continent diversion [B]: Continent cutaneous diversion, ureterosigmoidostomy and the newer variants of ureterosigmoidostomy. Bladder reconstruction [C]: native bladder remains in situ and is surgically manipulated to improve its function. Bladder replacement [D]: Native bladder was removed completely and a new reservoir was created, positioned where the native bladder used to be and connected to the native urethra, therefore, allowing patients to void in the natural way.

Treatment-related morbidity and mortality: Postoperative morbidity and mortality was lower for bladder replacement (14% and 1%, respectively) compared with ileal conduit diversion (21% and 2%, respectively). Trends for postoperative morbidity and mortality favour bladder replacement surgery when compared with ileal conduit and continent diversions, which might be attributable to better patient selection with younger and fitter patients undergoing bladder replacement. None of the differences reached statistical significance.

Table II. Clinical endpoints according to study design and UD type.

		A. Ileal conduit		B. Continent diversion		C. Bladder reconstruction		D. Bladder replacement	
		N = 8969		N = 13892		N = 7324		N = 16662	
	N studies	N/Total N (%)	Median % (Range)	N/Total N (%)	Median % (Range)	N/Total N (%)	Median % (Range)	N/Total N (%)	Median % (Range)
Postoperative morbidity									
Prospective	13	317/1175 (27)	21 (19-28)	32/275 (11.6)	11 (3-28)	1/21 (4.8)	5 (5-5)	54/470 (11.5)	14 (5-36)
Retrospective	134	555/2317 (24)	19 (0-62)	679/3896 (17.4)	17 (0-76)	183/1614 (11.3)	12 (0-41)	801/3784 (21.2)	18 (0-71)
Postoperative mortality									
Prospective	15	29/1159 (2.5)	2 (2-3)	43/1331 (3.2)	3 (0-5)	-	-	12/844 (1.4)	1 (0-7)
Retrospective	106	82/1911 (4.3)	3 (0-14)	159/3335 (4.8)	4 (2-24)	19/718 (2.6)	3 (0-18)	183/4575 (4.0)	2 (0-28)

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assessment: Quality of each study was assessed against a predetermined checklist addressing the quality of reporting, internal validity, and external validity. Each article assigned a score with a maximum achievable score of 27.

Authors only report on the prospective studies in the write-up.

Taken from the Nabi (2005) review for which this is an update: ***Continent diversion*** *strictly to mean continent cutaneous diversion, ureterosigmoidostomy and the newer variants of ureterosigmoidostomy*

Bladder reconstruction*: mean that the native bladder remains in situ and*

Note. Definition of diversions taken from Nabi et al. (2005) for which the Somani (2009) article is an update. Continent diversion [B]: Continent cutaneous diversion, ureterosigmoidostomy and the newer variants of ureterosigmoidostomy. Bladder reconstruction [C]: native bladder remains in situ and is surgically manipulated to improve its function. Bladder replacement [D]: Native bladder was removed completely and a new reservoir was created, positioned where the native bladder used to be and connected to the native urethra, therefore, allowing patients to void in the natural way.

Note: **Results on QoL are included in the Somani 2010 systematic review:**

Quality of life: 35 studies reported since 2003 with only 5 prospective. Most studies found no difference in overall quality of life, which was generally good for all types of transposed intestinal segment surgery. Of the 27 studies comparing ileal conduits to continent cutaneous diversions or neobladders, only 2 studies reported a better or marginally better quality of life with orthotopic bladder replacement. Mansson et al (2004) recognised the potential for bias in such reports and suggested neutral third party assessments. Mansson etl a. (2007) reported significant differences in quality of life between Swedish and Egyptian men in a prospective study using the FACT G and the FACTBL along with the HADS. Kulaksizoglu et al (2002) found that psychological and HRQOL return to baseline and stabilise after 12 months. *Of the 5 prospective studies:* 1 EORTC QLQ30/Beck Depression Inventory

1: SF36/FLZM
1: FACT BL/hospital anxiety and depression scale
1: Sickness impact profile/meta contrast technique
1: Interview method/MCT/visual analoge scale.

Adverse events: Operative complications in prospective studies seem to favour ileal conduit diversions. The lowest rate of operative complications was reported in the ileal conduit diversion group at 6%. The ileal conduit group reported the lowest reoperation rates (5%) with the highest rates reported after continent urinary diversion (9%). Rates of upper UTIs were highest in the ileal conduit group (26.5%) and lowest in the continent diversion group (8%). Bowel dysfunction (diarrhea, faecal leakage, faecal urgency, and incontinence), stoma complications and hernition are poorly reported for all types of procedures, with reports limited largely to retrospective studies.

Table III. Adverse events according to study design and UD type.

		A. Ileal conduit		B. Continent diversion		C. Bladder reconstruction		D. Bladder replacement	
		N = 8969		N = 13892		N = 7324		N = 16662	
	N studies	N/Total N (%)	Median % (Range)	N/Total N (%)	Median % (Range)	N/Total N (%)	Median % (Range)	N/Total N (%)	Median % (Range)
Operative complications									
Prospective	2	8/132 (6.1)	6 (3-36)	4/11 (36.4)	36 (36-36)	-	-	5/24 (20.8)	22 (8-36)
Retrospective	30	47/365 (12.9)	9 (0-40)	36/478 (7.5)	6 (0-22)	62/457 (13.6)	16 (4-60)	76/698 (10.9)	9 (0-46)
Need for reoperation									
Prospective	17	3/116 (2.6)	5 (2-9)	22/255 (8.6)	9 (3-13)	1/21 (4.8)	5 (5-5)	118/1335 (8.8)	7 (3-27)
Retrospective	190	270/1673 (16.1)	16 (1-71)	612/4524 (13.5)	13 (1-100)	431/2554 (16.9)	13 (2-48)	273/3817 (7.2)	8 (1-29)
Bowel anastomotic leakage									
Prospective	1	-	-	1/33 (3.0)	3 (3-3)	-	-	-	-
Retrospective	39	19/724 (2.6)	3 (0-8)	22/817 (2.7)	5 (0-12)	26/417 (6.2)	5 (2-13)	47/1835 (2.6)	4 (1-13)
Bladder/ureteroenteric anastomtic leakage									
Prospective	3	-	-	3/25 (12.0)	12 (12-12)	4/123 (3.3)	3 (3-3)	8/161 (5.0)	5 (5-5)
Retrospective	45	37/999 (3.7)	2 (0-14)	59/1271 (4.6)	4 (0-18)	7/345 (2.0)	4 (1-6)	136/2103 (6.5)	7 (1-24)
Upper tract UTI									
Prospective	14	13/49 (26.5)	23 (22-24)	29/389 (7.5)	8 (4-14)	2/21 (9.5)	10 (10-10)	24/272 (8.8)	14 (10-17)
Retrospective	101	167/3080 (5.4)	9 (1-36)	268/2647 (10.1)	9 (0-61)	81/571 (14.1)	11 (0-56)	105/3178 (3.3)	4 (0-26)
Lower tract UTI									

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is surgically manipulated to improve its function. While for the purpose of this article we only assessed surgical procedures that use intestinal segments as part of bladder reconstruction, e.g. augmentation cystoplasty or enterocystoplasty, we acknowledge that the true meaning also includes detrusor myomectomy or auto-augmentation.

Bladder replacement: *the native bladder was removed completely and a new reservoir was created, positioned where the native bladder used to be and connected to the native urethra, therefore, allowing patients to void in the natural way.*

Prospective	7	-	-	-	-	197/971 (20.3)	50 (35-83)	87/221 (39.4)	45 (10-64)
Retrospective	70	-	-	162/1178 (13.8)	12 (0-45)	194/1007 (19.3)	17 (0-61)	12/885 (14.1)	9 (1-85)
Clean intermittent self-catheterisation									
Prospective	9	-	-	18/25 (72)	72 (72-72)	164/294 (55.8)	64 (4-84)	48/495 (9.7)	10 (3-32)
Retrospective	83	-	-	299/351 (85.2)	93 (29-100)	904/1521 (59.4)	57 (0-100)	255/2772 (9.2)	9 (0-100)
Catheter blockage									
Prospective	2	-	-	1/50 (2.0)	2 (2-2)	8/86 (9.3)	17 (17-17)	-	-
Retrospective	15	-	-	18/416 (4.3)	5 (2-24)	17/115 (14.8)	16 (3-28)	29/1035 (2.8)	3 (0-29)
Diarrhea									
Prospective	3	10/76 (13.2)	13 (13-13)	17/151 (11.3)	10 (9-12)	-	-	-	-
Retrospective	36	9/210 (4.3)	2 (0-6)	104/1218 (8.5)	5 (0-34)	42/361 (11.6)	9 (3-76)	57/1013 (5.6)	1 (0-43)
Stress incontinence									
Prospective	15	-	-	7/278 (2.5)	6 (1-8)	-	-	22/680 (3.2)	3 (0-7)
Retrospective	54	1/20 (5)	5 (5-5)	30/864 (3.5)	5 (0-10)	49/480 (10.2)	10 (0-26)	152/1986 (7.7)	6 (0-31)
Odor									
Prospective	2	23/34 (67.6)	68 (68-68)	6/21 (28.6)	29 (29-29)	-	-	-	-
Retrospective	3	34/58 (58.6)	59 (59-59)	5/65 (7.7)	8 (8-8)	-	-	2/50 (4)	4 (4-4)
Stomal stenosis									
Prospective	2	-	-	9/81 (11.1)	11 (10-12)	-	-	-	-
Retrospective	88	81/1860 (4.4)	6 (0-18)	399/4057 (9.8)	7 (0-45)	157/966 (16.3)	9 (0-34)	-	-
Hernia retrospective	35	45/1227 (3.7)	4 (0-18)	55/2220 (2.5)	36 (0-18)	1/12 (8.3)	8 (8-8)	9/514 (1.8)	2 (1-4)
Faecal urgency retrospective	5	2/29 (0)	0 (0-0)	10/258 (3.9)	3 (2-5)	5/89 (5.6)	7 (3-12)	-	-
Faecal incontinence retrospective	5	2/29 (0)	0 (0-0)	22/221 (10)	32 (3-61)	10/74 (13.5)	12 (8-17)	-	-
Flatus leakage retrospective	2	5/100 (5)	3 (3-3)	-	-	8/28	15 (15-15)	-	-
Constipation retrospective	7	9/122 (7.4)	5 (1-10)	-	-	10/55 (18.2)	18 (17-19)	15/126 (11.9)	3 (0-24)

Note. UTI indicates urinary tract infections. Definition of diversions taken from Nabi et al. (2005) for which the Somani (2009) article is an update. Continent diversion [B]: Continent cutaneous diversion, ureterosigmoidostomy and the newer variants of ureterosigmoidostomy. Bladder reconstruction [C]: native bladder remains in situ and is surgically manipulated to improve its function. Bladder replacement [D]: Native bladder was removed completely and a new reservoir was created, positioned where the native bladder used to be and connected to the native urethra, therefore, allowing patients to void in the natural way.

As shown in Table IV, of the prospective studies reporting physiological and radiological outcomes 14 studies described upper tract dilatation in 10% of continent diversion patients and 10% of bladder replacement patients. For all procedures, the reported incidence of ureterointestinal stricture was between 5 and 11% . The renal failure rate varied from 3-7% and the metabolic acidosis rate varied from 26-45%. The median reported incidence for urinary stone disease was 15, 25 and 5% for continent diversion, bladder reconstruction and bladder replacement, respectively.

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Table IV. Physiological and radiological outcomes according to study design and UD type.

		A. Ileal conduit N = 8969		B. Continent diversion N = 13892		C. Bladder reconstruction N = 7324		D. Bladder replacement N = 16662	
	N studies	N/Total N (%)	Median % (Range)	N/Total N (%)	Median % (Range)	N/Total N (%)	Median % (Range)	N/Total N (%)	Median % (Range)
Upper tract dilation									
Prospective	14	-	-	37/423 (8.7)	10 (5-24)	-	-	126/1022 (12.3)	10 (2-35)
Retrospective	119	192/1482 (13)	11 (0-74)	204/2374 (8.6)	7 (0-61)	201/884 (22.7)	6 (0-92)	351/3490 (10.1)	9 (0-100)
Uterointestinal stenosis									
Prospective	19	14/126 (11.1)	11 (9-12)	35/488 (7.2)	8 (5-17)	1/665 (0.15)	17 (17-17)	48/958 (5)	7 (3-18)
Retrospective	134	131/1625 (8.1)	7 (1-100)	356/4591 (7.8)	7 (0-52)	60/796 (7.5)	7 (0-24)	292/4972 (5.9)	5 (0-40)
Renal failure									
Prospective	8	-	-	11/295 (3.7)	4 (2-20)	18/123 (6.5)	15 (15-15)	3/105 (2.9)	2 (0-13)
Retrospective	91	76/1744 (4.4)	3 (0-38)	63/2165 (2.9)	2 (0-36)	113/931 (12.1)	2 (0-45)	121/3012 (4.0)	1 (0-18)
Metabolic acidosis									
Prospective	9	-	-	127/398 (31.9)	33 (2-60)	182/689 (26.4)	29 (1-78)	95/209 (45.5)	40 (31-50)
Retrospective	117	18/585 (3.1)	4 (0-13)	492/2380 (20.7)	14 (0-100)	135/1071 (12.6)	11 (0-44)	381/2466 (15.5)	5 (0-70)
Metabolic alkalosis									
Retrospective	16	24/101 (23.8)	26 (0-51)	2/252 (0.8)	14 (14-14)	10/254 (3.9)	6 (0-9)	0/193 (0)	0 (0-0)
Urinary stones									
Prospective	10	-	-	8/56 (14.3)	15 (14-17)	161/689 (23.4)	25 (17-42)	25/682 (3.7)	5 (0-10)
Retrospective	138	90/1720 (5.2)	5 (1-31)	466/4574 (10.2)	8 (0-80)	322/2748 (11.7)	11 (2-42)	165/2791 (5.9)	7 (1-16)
Vitamin B12 deficiency									
Prospective	2	-	-	2/138 (1.4)	5 (0-10)	-	-	-	-
Retrospective	29	9/157 (5.7)	7 (3-15)	45/721 (6.2)	5 (0-31)	5/152 (3.3)	3 (0-14)	26/497 (5.2)	5 (0-29)
Bone disease									
Retrospective	8	19/27 (70.4)	70 (70-70)	37/496 (7.5)	5 (0-21)	8/25 (32)	32 (32-32)	7/201 (3.5)	5 (3-8)

Note. Definition of diversions taken from Nabi et al. (2005) for which the Somani (2009) article is an update. Continent diversion [B]: Continent cutaneous diversion, ureterosigmoidostomy and the newer variants of ureterosigmoidostomy. Bladder reconstruction [C]: native bladder remains in situ and is surgically manipulated to improve its function. Bladder replacement [D]: Native bladder was removed completely and a new reservoir was created, positioned where the native bladder used to be and connected to the native urethra, therefore, allowing patients to void in the natural way.

Comments

Selection of articles:
- References for the included studies not reported.
- No information provided on extraction and appraisal differences between observers.
- Authors concentrate on the outcomes from prospective studies only.

Integrity of review:
- Possible that some studies included patients with diseases other than bladder cancer (no information presented on patient characteristics so no way of establishing breakdown).
- No definition for each type of UD, how does bladder reconstruction differ to bladder replacement – I took the definitions from the Nabi (2005) review.

Somani, BK et al. "How Close Are We to Knowing Whether Orthotopic Bladder Replacement Surgery Is the New Gold Standard?-Evidence From a Systematic Review Update." Urology 74.6 (2009): 1331-1339.

Objective of review: Consider the clinical effectiveness and risk profile of the different types of surgeries using transposed intestinal segments.

	– Use of different instruments to measure QoL makes it impossible to compare cohorts. – No information on whether the complications reported are reported with standardised measures. – Many studies included did not use a standardised method for reporting complications. *Statistical analysis:* – Numbers in Table I do not add up to the numbers presented in the text for total number of participants (total if you add up all patients: 47442 versus total reported: 46921). Also if you add up the total N at the top of the column for each UD these do not add up to the total reported in the text (46847 versus 46921). – Authors allude in the comment to the fact that 'none of the differences reached statistical significance' but unclear if this is all data, how was this computed?

Somani, BK et al. "Quality of Life With Urinary Diversion." European Urology, Supplements 9.10 (2010): 763-771.

Objective of review: Assess the evidence for quality of life following transposed intestinal segment surgery.

Pub year: 2010		**Review Methods**	**Results**
Search Period	1966 – August 2010	**Inclusion criteria:** All relevant English-language articles on QoL reports on patients having transposed intestinal segment surgery. **Search engines:** MEDLINE, PUBMED, EMBASE, CINAHL, Cochrane Library. **Data extract and study appraisal:** No information provided. **Quality assessment:** Authors describe differences between study design, selection biases and whether validated QoL instruments are used.	**HRQOL:** Of the 46 included publications, 8 were prospective studies and 38 were retrospective. Table I shows the breakdown of measures used in the included studies. Sixteen studies used two different QoL assessment tools. Thirty of the 46 studies (65%) were from Europe with Sweden contributing 9 studies.
Abstracts reviewed	No information provided.		
Studies included	46		
Study designs	8: Prospective 38: Retrospective		
Participants of included studies	4,186		
Countries of included studies	9: Sweden 8: Japan 8: United States 5: Denmark 4: United Kingdom 3: Germany 2: Italy 2: Norway 1: The Netherlands 1: Canada 1: Austria		

Table I. Measures of Quality of Life used in the review.

Measures	N
Patient interview	7
Self-designed non-validated questionnaire	11
Validated questionnaire	
SF-36	9
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ)	8
Functional Assessment of Cancer Therapy Bladder Cancer (FACT-BL)	5
Bladder Cancer Index (BCI)	2
Schedule for Evaluation of Individual Quality of Life (SEIQoL)	1
Beck Depression Inventory (BDI), Profile of Mood States (POM)	1
Sickness Impact Profile (SIP)	2

Table II-VI. Key findings from of all quality of life studies after radical cystectomy and ileal conduit (IC), continent cutaneous diversion (C) or neobladder diversions (NB), 1966 to August 2010.

Table II. No difference between groups, no information on level of QoL (e.g. high/low)/satisfaction: N = 15

Study	Year	IC	CD	BR	Conclusion on QoL
Prospective					
Yuh	2009	34	-	-	Pre-post cystectomy QoL: postoperative QoL scores similar at 3 months and exceeded baseline at 6 months.
Kulaksizoglu	2002	49	2	15	Psychological and HRQoL measures come to baseline values and stabilise after 12 months
Retrospective					
Filipas	1997	27	54	-	No difference in global satisfaction and health; diversion type must consider psychological & employment status
Bjerre	1997	20	17	-	No difference in two groups
Bjerre	1998	27	-	49	No difference in two groups

Somani, BK et al. "Quality of Life With Urinary Diversion." European Urology, Supplements 9.10 (2010): 763-771.

Objective of review: Assess the evidence for quality of life following transposed intestinal segment surgery.

	1: Turkey 1: Greece		
Funding source	Authors have nothing to disclose. No funding support.		

Fujisawa	2000	20	-	36	No difference in two groups
Mansson	2002	-	35	29	No difference overall (BR: more incontinence, but better appreciation of appearance & erectile function)
Yoneda	2005	-	-	48	No difference in HRQoL between patients and controls
Allareddy	2006	56	-	26	No difference between IC and BR; no major difference between noncystectomy and cystectomy patients
Sogni	2008	53	-	32	No difference in QoL or complications and survival.
Autorino	2008	44	-	35	No significant difference in scores between IC and BR. Compared to control population: physical, social, and emotional functioning worse in both IC and BR groups.
Kitamura	1999	36	22	21	Little difference in all groups; patients accepted and adapted to present status
Protogerou	2004	58	-	50	QoL same in both groups. Higher emotional function compared with normal population but more urinary & sexual problems.
Kikuchi	2006	20	14	15	QoL: no difference; body image and urinary function affected. 10/13 IC, 7/9 CD and 6/7BR would choose same operation again.
Saika	2007	56	31	22	No difference in HRQoL; more patients disappointed with BR

Note. IC: ileal conduit. CD: continent diversion. BR: orthotopic bladder replacement.

Table III. Good QoL/global satisfaction: N = 12

Study	Year	IC	CD	BR	Conclusion on QoL
Prospective					
Hardt	2000	24	20	-	High global satisfaction with both diversions: 75% would choose same diversion again
Mansson	1998	17	22	18	Patients with wet stoma did not do less well than continent procedures, and the adjustment improved with time.
Retrospective					
Bjerre	1994	50	26	-	Global satisfaction high and similar in both groups.
Weijerman	1998	-	23	33	Overall QoL favourable in both groups
Hart	1999	24	93	103	Good overall QoL in all groups.
Hara	2002	37	-	48	Patients satisfied with overall QoL and health status in both groups
Fossa	1987	59	-	-	Good QoL
Nordstrom	1992	66	-	-	80% overall good health, 70% unchanged social activity; reported on body image in females
Sullivan	1998	-	42	44	Good overall QoL; significant effect on sex life; 70% patients had no limits on activities
Chadwick	1990	41	-	-	83% improved QoL; 90% continue household duty; leakage problem
Bjerre	1995	29	-	38	High global satisfaction with both IC and BR; urinary leak more frequent in BR but IC patients affected more.
Frich	2009	37	-	35	All patients rated their QoL as high with no significant difference between them. More patients in BR group experienced practical problems compared with IC. Influence on everyday life was significantly better in favour of IC compared with BR.

Note. IC: ileal conduit. CD: continent diversion. BR: orthotopic bladder replacement.

Table IV. Differences between groups/problems/reduced QoL: N = 13

Study	Year	IC	CD	BR	Conclusion on QoL
Prospective					
Hedgepeth	2010	85	-	139	Longest follow-up: 8 year. Initial worsening of body image in both groups. Earlier return of body image to baseline for IC, with BR never returning to baseline. Age but not sex associated with body image with older patients having better body image (study had 112 controls).

Somani, BK et al. "Quality of Life With Urinary Diversion." European Urology, Supplements 9.10 (2010): 763-771.

Objective of review: Assess the evidence for quality of life following transposed intestinal segment surgery.

Retrospective						
Jones	1980	34	-	-	Stoma problems	
Mansson	1988	40	20	-	Fewer stoma problems and more freedom for activities in CD	
Gerharz	1997	131	61	-	Fewer stoma problems in CD; overall scores similar	
Okada	1997	63	74	-	Fewer stoma problems in CD, but more night catheterisations, more satisfied patients in CD; counselling/consent	
McGuire	2000	38	16	38	IC patients have decreased mental QoL but continent diversions do not, compared to population norms.	
Hobisch	2000	33	-	69	QoL better with BR in all domains	
Dutta	2002	23	-	49	BR marginally better when adjusted for age, stage, and sex	
Philip	2009	24	-	28	BR patients were younger and fitter. HRQoL was favourable in both groups, with physical functioning significantly better in BR group. Conclusion: Body image issues persist although no formal body image measures used.	
Gilbert	2007	66	-	122	More urinary leak with BR	
Nordstrom	1992	66	-	-	90% men impotent, 5/6 women lower sexual activity.	
Mansson	1991	20	14	-	Postoperative sexual problems; lack of psychological support from health services regardless of diversion.	
Miyake	2010	-	-	80	HRQoL similar except physical health, emotional problems and bodily pain that was worse in BR patients. No difference between men and women.	

Note. IC: ileal conduit. CD: continent diversion. BR: orthotopic bladder replacement.

Table V. Interventions: N = 4

Study	Year	IC	CD	BR	Conclusion on QoL
Prospective					
Mansson	1997	17	17	16	Defensive strategies and philosophical outlook generally did not influence the psychosocial outcome of intervention.
Somani	2009	29	-	3	Non HRQOL measures can help in counselling patients for decision making before surgery. Body image not an important determinant of QoL and does not influence patient preferences for the type of transposed intestinal segment surgical option.
Retrospective					
Mommsen	1989	68	-	-	Preoperative counselling results in improvement but often neglected
Boyd	1987	87	85	-	Preoperative counselling improved patients' overall satisfaction but more for CD

Note. IC: ileal conduit. CD: continent diversion. BR: orthotopic bladder replacement.

Table VI. Cross country comparison: N = 1

Study	Year	IC	CD	BR	Conclusion on QoL
Prospective					
Mansson	2007	-	-	61	Swedish men had better FACT-BL and HADS score: patients assessed outcome differ with different populations

Note. IC: ileal conduit. CD: continent diversion. BR: orthotopic bladder replacement.

Somani, BK et al. "Quality of Life With Urinary Diversion." European Urology, Supplements 9.10 (2010): 763-771.

Objective of review: Assess the evidence for quality of life following transposed intestinal segment surgery.

Comments

Selection of articles:
- No information on number of articles found from the search and how many reviewed/excluded.
- Unclear if all patients in the included studies all had bladder cancer.
- 1 paper extracted was not included in the evidence table (Henningsohn, 2003).
- Sogni reference reports incorrect number of patients who completed the QoL measures (should be IC: 18 and ONB:16).

Integrity of review:
- Limited assessment of the study quality.

Statistical analysis:
- No attempts to compare data, results are presented as main finding/conclusion of each paper.
- Unclear if the differences presented in the results section are significant in the original studies.

Metcalfe, M. et al. "Association between urinary diversion and quality of life after radical cystectomy." Canadian Journal of Urology 20.1 (2013): 6626-6631.

Pub year: 2013		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Canada	*Inclusion criteria:* Consecutive database of patients treated with radical cystectomy from 2000-2006 (n=314). 168 of the 314 patients (53.5%) were alive in 2008. 84/168 (50% of alive patients) responded to survey. Authors report comparison between non-responders and responders for baseline characteristics. (More ICUD in non-responder group [p=0.02]). As shown in Table I IC responders were significantly older compared to ON patients. In addition, there were more females IC responders compared to ON responders. The IC and ON responders did not significantly differ on any health related variables (see Table I). *Table I. Demographic and health status of patients.*	Self-administered Functional Assessment of Cancer Therapy-Vanderbilt cystectomy index (FACT-VCI) FACT-VCI (44 questions) consists of a radical cystectomy specific section (17 questions) and a FACT-general section (27 questions) Comorbidity assessed using the Adult Comorbidity Evaluation-27 instrument FACT-VCI mailed	Ileal conduit (IC) *versus* Orthotopic neobladder (ON)	HRQOL	ON participants reported significantly higher FACT-VCI scores compared to IC participants. A trend ($p<0.1$) was reported for higher radical cystectomy-specific scores for the ON participants compared to the IC participants. There were no significant differences between the UD groups for any other QoL domain (see Table II). *Table II. Univariate analysis of UD and QoL.*
Design, period	Retrospective cohort study 2008					
N	84					
Follow-up	Median: 5.6 years Range: 2.1-9.3 years					
Funding source	No information provided					

	Ileal conduit (IC)	Orthotopic neobladder (ON)
N (84)	53	31
Mean age**	**68**	**62**
Female*	**11**	**1**
Male	42	30
Comorbidity		
None/mild	21	11
Moderate	21	16
Severe	11	4

Variable	Overall N=84	IC n=53	ON n=31	P
FACT-VCI	79	**76**	**82**	**0.03**
Radical cystectomy-specific	28	27	29	0.05
FACT-General	51	50	52	0.13
Social/family well being	20	19	21	0.19
Physical well being	4	4	4	0.47
Emotional well being	6	7	6	0.34

Multivariate analysis showed no independent association between the type of UD and QoL (for FACT-VCI and Radical cystectomy specific scale). Age was independently associated with increased radical cystectomy-specific QoL issues (see Table III).

Table III. Multivariate linear regression analysis of UD and QoL.

	FACT-VCI		Radical cystectomy-specific	
Variable	β	95% CI	β	95% CI
Age	-0.2	-0.5 to 0.1	**-0.2**	**-0.4 to -0.1***
Gender	2.9	-5.0 to 10.9	0.6	-4.0 to 5.2
Comorbidity	-0.5	-3.6 to 2.5	0.9	-0.9 to 2.7
Duration of follow-up	0.3	-1.5 to 1.0	-0.1	-0.8 to 0.6
pTstage	-2.7	-8.6 to 3.2	1.0	-4.5 to 2.4

Metcalfe, M. et al. "Association between urinary diversion and quality of life after radical cystectomy." Canadian Journal of Urology 20.1 (2013): 6626-6631.

		Adj. chemo: 8 / 16 Length stay *(days)*: 15 / 14 Est. blood loss *(mL)*: 1027 / 1042 Pathologic T stage ≤T2: 37 / 26 ≥T3: 16 / 5 *Note.* *p<0.05, **p<0.01.	in November 2008 to 168 UD patients. Follow-up call 6 weeks later to non-responders.			Type of UD: 4.0 / -1.9 to 10.0 / 1.5 / -1.9 to 4.9 *Note.* *p<0.05.	
Comments	*Selection bias:* – Low response rate (50%, authors acknowledge this limitation), with over half the database of UD patients deceased at time of the survey. Non-responders compared to responders. – Author's state that the choice of type of UD recommended to patients was a complex decision and may have been influenced by many factors that could also impact QoL (e.g. Comorbidity status). *Integrity of intervention:* – Authors do not state how to interpret the FACT-VCI (i.e. higher scores = higher QoL). FACT-VCI total mean scores appear high in comparison to Anderson et al (2012) who stated that the range for the scale was 0-68, Metcalfe reports 168 points (seems to have totalled the sub-scales). Also different interpretation of the scale compared to Gacci et al (2013) who reported that lower scores matches to higher HRQOL. *Statistical analysis:* – Missing values were imputed but no information on how many missing. – Inconsistencies in reporting of numbers in the methods section (e.g. numbers of responders by UD differ for responders in Table 1 and 2) makes it unclear how many participants had ICUD and ONUD in the responder group.						

Gacci, M. et al. "Quality of life in women undergoing urinary diversion for bladder cancer: results of a multicenter study among long-term disease free survivors." Health and Quality of Life Outcomes (2013): 11; 43.

Pub year: 2013		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Italy	*Inclusion criteria:* Disease free female patients (≥ 18 years of age) who underwent RC and UD for clinically localized bladder cancer in two urological institutions from Jan 2000 – Dec 2008 without any evidence of tumor recurrence ≥36 months since surgery. *Exclusion criteria:* Patients with major concomitant medical or psychological diseases, including those with remarkable bowel disease and those with previous lower tract surgery (with the exception of staging TURBT). Patients previously treated with neoadjuvant chemotherapy or radiation therapy were excluded. N=37/41 enrolled patients 4 patients excluded: *1 had serious inflammatory bowel disease, 3 had previous lower tract genitourinary surgery.*	European Organisation for Research and Treatment of Cancer generic (EORTC QLQ-C30) 30-item questionnaire. Scores linearly transformed to a 0-100 scale. Lower score matches to higher HRQOL EORTC bladder cancer specific survey (EORTC QLQ-BLM30) 30- item questionnaire. Scores linearly transformed to a 0-	Continent Orthotopic Neobladder (ONB-VIP) *versus* Cutaneous ureterostomy (CUS) *versus* Ileal conduit	HRQOL	Only the more remarkable subscores of all questionnaires were reported. As seen in Table III a trend was reported toward worse HRQL for "appetite loss" and "fatigue" among CUS patients compared with BK-IC or ONB-VIP participants. **CUS reported significantly worse "physical well-being" and "emotional well-being"** compared to BK-IC or ONB-VIP. **No other differences in questionnaire results among the three UD groups were reported.** *Table III. Average scores of any considerable*
Design, period	Retrospective cohort study No info on study period only that it was a minimum of 36 months after surgery					

Gacci, M. et al. "Quality of life in women undergoing urinary diversion for bladder cancer: results of a multicenter study among long-term disease free survivors." Health and Quality of Life Outcomes (2013): 11; 43.

N

37

Follow-up

Mean: 60.1 months
Range: 36-122 months

Funding source

Author(s) declare no competing interests

Mean age at surgery was 67.3 (SD: 8.7) years. As shown in Table I and Table II all groups were similar according to clinical, pathological and perioperative characteristics.

Table I. Age according to UD and total comorbidity count.

	Total	CUS	Bricker	VIP
N	37	12	16	9
Mean age at follow-up (SD)	73.1 (8.7)	75.3 (10.8)	74.4 (8.8)	71.8 (7.0)
Comorbidity				
0	24			
1-2	4			
3	9			

Note. Clavien-Dindo classification used for perioperative complications. Authors calculated each patient's Charlson Comorbidty Index.

Table II. Pathologic T Stage classification according to UD.

Pathologic T stage (%)	CUS	Bricker	VIP
pT1/Tis	4	6	0
pT2	3	7	4
pT3	5	3	5

100 scale. Lower score matches to higher HRQOL

Functional Assessment of Cancer Therapy-BL (FACT-BL) and FACT-G. The FACT-BL and FACT-G plus 17 additional questions created the Functional Assessment of Cancer Therapy Vanderbilt cystectomy index [FACT-VCI]. Lower score matches to higher HRQOL

All questionnaires were self-administered during a scheduled follow-up visit (participants had help filling the questionnaire in if it was needed). Data on clinical, pathological and perioperative characteristics were taken from clinical records.

urinary diversion (BK-IC)

specific subscales of questionnaires, stratified according to different UD.

	Subscale	CUS	BK	VIP
EORTC QLQ C30	Total (SD)	28.1 (8.7)	21.5 (6.2)	23 (2.2)
	Physical function	1.8	1.3	1.4
	Diarrhea	2.5	1.0	1.0
	Appetite loss^{+}	**1.5**	**1.1**	**1.1**
	Fatigue^{+}	**2.0**	**1.5**	**1.6**
EORTC QLQ BLM30	Total (SD)	7.3 (2.6)	6.8 (2.0)	6.7 (2.0)
	Body Image	2.3	2.0	1.4
	Sexual function	0.6	0.5	0.3
FACT-BL	Total (SD)	7.8 (2.3)	6.2 (2.1)	7.1 (1.4)
	Social well-being	1.9	2.0	2.1
	Functional well-being	1.8	2.0	2.0
	Physical well-being**	**1.3**	**0.6**	**0.7**
	Emotional well-being*	**1.7**	**1.2**	**1.3**

Note. $^{+}$p<0.1, *p<0.05, **p<0.01.

Comments

Selection bias:
- Small sample size
- It is unclear whether the 41 patients enrolled were all eligible patients at the two institutions.
- Patients with psychological diseases were excluded but authors do not state what constituted a psychological disease and how they assessed this in potentially eligible participants. Also, unclear if any participants were excluded due to a psychological disease.
- Unclear how many patients were not eligible – authors state that they have removed biases of patients with initial postoperative worse HRQOL and/or the fear for tumor recurrence after RC but how selective is the sample included?

Data collection methods:
- No missing data
- Participants had help filling the questionnaire in if it was needed – no information presented on how many required help and whether there were questions that participants found difficult to answer?
- Participants completed survey during a scheduled follow-up visit but unclear where they completed the survey (e.g. waiting room or their doctor's office) and whether this may have had an impact on their responses.

Integrity of intervention:
- All enrolled patients were able to ply the study design, including to self-compile the selected questionnaires – what does this mean?
- FACT-VCI total mean scores appear high in comparison to Anderson et al (2012) who stated that the range for the scale was 0-68, Metcalfe reports 168 points (seems to have totalled the sub-scales). Also different interpretation of the scale compared to Gacci et al (2013) who reported that lower scores matches to higher HRQOL. Appears total number of questions is different in this article compared to Metcalfe.
- No information on what constitutes good/bad HRQOL

Statistical analysis:
- Univariate analysis only, did not control for potential confounding variables. Authors must have conducted large number of univariate analyses on relative small sample sizes in each UD group – may increase error rates, should have considered multivariate analyses.
- Only the more remarkable sub-scores of all questionnaires are reported but it is unclear what constitutes remarkable.

Gacci, M. et al. "Quality of life in women undergoing urinary diversion for bladder cancer: results of a multicenter study among long-term disease free survivors." Health and Quality of Life Outcomes (2013): 11; 43.	
	– Total scores are very low for EORTC QLQ BLM 30 and FACT-BL – suggestive of "very" good QoL? – Unclear if statistical analyses were conducted on the demographic variables (authors state groups were similar).

Erber, B et al. "Morbidity and quality of life in bladder cancer patients following cystectomy and urinary diversion: a single institution comparison of ileal conduit versus orthotopic neobladder." International Scholarly Research Network Urology (2012): 342796.

Pub year: 2012		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Germany	Authors selected potential participants from a database of patients with bladder cancer (n=301) who underwent radical cystectomy with UD between Jan 1993 – Aug 2007. *Inclusion criteria:* All patients with bladder cancer who underwent radical cystectomy with either ileal conduit (IC) or ileal neobladder (IN) between Jan 1993 – Aug 2007 for whom there were no death data in 2008 (n=126). *Exclusion criteria:* Due to small sample sizes in other types of UD authors excluded all patients with bladder cancer (n=40) who underwent radical cystectomy with all other types of UD (e.g. Mainz pouch I, ureterocutaneostomy). In addition, deceased patients with bladder cancer who underwent radical cystectomy with either IC or IN between Jan 1993 – Aug 2007 (n=135). N=58/126 (46% response rate) responded to survey. Demographic data was reported for sample of patients who had undergone radical cystectomy with selected types of UD (n=261) but not for the respondents who completed the QoL survey (n=58).	European Organisation for Research and Treatment of Cancer generic (EORTC QLQ-C30) 30-item questionnaire. EORTC bladder cancer specific survey (EORTC QLQ-BLM30) 30-item questionnaire. Scores linearly transformed to a 0-100 scale. For the functional items: higher scores = higher	Ileal conduit (IC) *versus* Ileal neobladder (IN)	HRQOL	As shown in Table II the global health status/QoL ($p<0.05$) and physical functioning ($p<0.05$) were rated significantly higher by IN participants compared to IC participants. Diarrhoea occurs significantly more often in IN participants compared to IC participants ($p<0.01$). No measure of sexual functioning due to low response rates to these questions. *Table II. Average scores and standard deviation (SD) of the QLQ-C30 functional scales, symptom scales and single items according to UD.* IC (n=24) / IN (n=34) ***Functional scales*** Mean (SD) / Mean (SD) **Global health status/QOL*** **58.0 (25.3)** / **72.3 (19.5)** **Physical functioning*** **65.8 (29.4)** / **82.6 (19.9)** Role functioning 63.8 (31.1) / 76.0 (27.9) Emotion functioning 72.2 (22.3) / 81.1 (22.3) Cognitive functioning 77.8 (22.9) / 83.3 (20.5) Social functioning 65.3 (32.2) / 70.1 (33.0) ***Symptoms scales*** Fatigue 37.5 (28.1) / 26.0 (28.3) Nausea and vomiting 9.7 (20.2) / 3.4 (12.8)
Design, period	Retrospective cohort study 2008					
N	58					
Follow-up	Mean IC: 33.2 months (SD: 32.8) Mean IN: 50.6 months (SD: 45.0)					

Erber, B et al. "Morbidity and quality of life in bladder cancer patients following cystectomy and urinary diversion: a single institution comparison of ileal conduit versus orthotopic neobladder." International Scholarly Research Network Urology (2012): 342796.

Funding source	No information provided		level of functioning. For the symptoms/single items: higher score = higher level of symptomatology/ problems. Written inquiry to complete self-administered questionnaire.			

Pain	26.4 (31.8)	18.6 (34.0)
Single items		
Diarrhoea**	**4.2 (14.9)**	**23.5 (31.3)**
Dyspnoea	37.5 (35.9)	27.5 (37.1)
Insomnia	29.2 (31.6)	21.6 (27.1)
Appetite loss	18.1 (31.1)	6.9 (17.9)
Constipation	22.2 (30.6)	11.8 (19.9)
Financial difficulties	25.0 (35.8)	20.6 (32.8)

Note. *p<0.05, **p<0.01. N for the global health status/QoL for the IC group was 23.

Comments	*Selection bias:* – Small sample size and a low response rate to survey with over half the database of UD patients deceased at time of the survey. *Data collection methods:* – Authors state that there was no missing data however, in the results section they say that sexual functioning could not be analysed because an altogether insufficient number of patients answered these questions. – No demographic data for sample, no comparisons to non-responders.

Vakalopoulos, I et al. "Does intubated uretero-ueterocutaneostomy provide better health-related quality of life than orthotopic neobladder in patients after radical cystectomy for invasive bladder cancer" International Urology and nephrology (2011): 43(3): 743-748.

Pub year: 2011		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Greece	*Inclusion criteria:* All patients who underwent radical cystectomy due to invasive bladder cancer and UD from April 2008-September 2009 and (after full description) accepted the proposal to participate in the study by signing a consent form. *Exclusion criteria*: Use of neo-adjuvant and/or adjuvant chemotherapy, local or metastatic recurrence of bladder cancer, and preoperative medical history of psychiatric	Beck depression Inventory (BDI). Range 0-64. 21 questions. Points between 14-20 show moderate depressive status and those ≥21 severe	Uretero-ureterocutaneo-stomy (UUS) *versus* Orthotopic neobladder (ONB)	HRQOL	No statistically significant differences for the scores of FACT-G, FACT-VCI and BDI between the two groups. As shown in Table I, a trend was found for higher VCI scores in the UUS group compared to the ONB participants (p=0.05). For the SF-36 scale, UUS participants reported higher Role-emotional scores compared to ONB participants (p=0.02). *Table I. Comparison of scale scores in the two UD groups.*
Design, period	Retrospective cohort study 2010					
N	39					

	ONB n=25	UUS n=14	P value
	Mean (SD)	Mean (SD)	
FACT-G	80.8 (14.6)	86.6 (9.3)	0.18
VCI[+]	**41 (8.8)**	**46 (9.2)**	**0.05**

Vakalopoulos, I et al. "Does intubated uretero-ueterocutaneostomy provide better health-related quality of life than orthotopic neobladder in patients after radical cystectomy for invasive bladder cancer" International Urology and nephrology (2011): 43(3): 743-748.

Follow-up	Median: 17 months Range: 7-84 months	disorders and/or psychiatric medication. Type of UD was chosen randomly. However, patients with cancer lesions at the bladder neck, renal dysfunction (creatinine clearance <50mg/dl), and impaired heart function (ejection fraction <45%) were excluded from candidates for ONB. N = 39 patients (35 men and 4 women) Mean age = 66.95 (±8.2) years old 25 Orthotopic neobladder (ONB) 14 Uretero-ureterocutaneostomy (UUS) No statistically significant difference in age, socioeconomic class and time from operation to completion of the questionnaire between the two UD groups. All patients had muscle invasive urothelial tumour, without local or recurrent metastasis.	depressive status. Patients whose score is ≥17 show the need for psychiatric treatment. Functional Assessment of Cancer Therapy Scale-General (FACT-G). Range 0-108 FACT-VCI. Range 0-176 Short Form (SF)-36 Face-to-face interview			FACT-VCI 12.8 (21.5) 132.6 (17.4) 0.11 BDI 8.3 (6.3) 7.4 (7.9) 0.55 SF-36 PCS (physical health) Physical functioning 69.4 (30.3) 80 (24.9) 0.26 Role-physical 46.9 (46.2) 76.8 (42.1) 0.06 Bodily pain 81.1 (28.3) 88.4 (15.0) 0.87 General health 55.4 (15.0) 56.8 (11.7) 0.77 MCS (Mental health) Vitality 59.0 (21.3) 59.3 (9.6) 0.95 Social functioning 75 (24.2) 85.7 (20.7) 0.14 **Role-emotional* 53.3 (46.2) 88.1 (28.1) 0.02** Mental health 63.2 (16.1) 60.6 (13.5) 0.47 *Note.* $^{+}$p<0.1, *p<0.05. Nine patients had a score >14 on the BDI questionnaire, indicating depressive syndrome. Depressed patients had statistically significant lower scores than non-depressed participants on the SF-36 PCS and MCS (p<0.05). Negative correlation of FACT-G and FACT-VCI scores with BDI score (*r*= -0.527, p<0.001 and *r*= -0.538, p<0.001, respectively).
Funding source	Authors declare that there is no conflict of interest from the study.					
Comments	*Selection bias:* – Small sample size – Authors provide no information on how many patients were excluded, how many patients did not accept the proposal to participate. – Authors excluded patients with preoperative medical history of psychiatric disorders and/or psychiatric medication but no information on what this constituted (e.g. depression?). *Data collection methods:* – Authors state the selection of UD was randomly assigned but then state a number of contraindications as to why some participants were not eligible for ONB. *Integrity of intervention:* – FACT-VCI total mean scores are different in comparison to Anderson et al (2012) who stated that the range for the scale was 0-68, Metcalfe reports 168 points (seems to have totalled the sub-scales). Also different interpretation of the scale compared to Gacci et al (2013) who reported that lower scores matches to higher HRQOL. Appears total number of questions is different in this article compared to Metcalfe. – No information on how to interpret the HRQOL scales – higher scores means more or less HRQOL.					

Sherwani, A. et al. "Comparative study of various forms of urinary diversion after radical cystectomy in muscle invasive carcinoma urinary bladder" International Journal of Health sciences, Qassim University (2009): 3(1); 1430H.

Pub year: 2009	**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**

Sherwani, A. et al. "Comparative study of various forms of urinary diversion after radical cystectomy in muscle invasive carcinoma urinary bladder" International Journal of Health sciences, Qassim University (2009): 3(1); 1430H.

Country	India	All patients with urinary bladder muscle invasive carcinoma treated with standard radical cystoprostatectomy in males and anterior exenteration in females with reconstruction with UD between Jan 2003 – Oct. 2007. N=30 (28 men, 2 women). All patients had transitional cell carcinoma (TCC) documented histologically on trans-urethral biopsies. *Table I. Total demographics of sample and according to UD.* Total / Ileal conduit (IC) / Mainz pouch II (MPII) / Ileal neobladder (IN) N: 30 / 13 / 13 / 4 Mean age: 57.7 / 59 / 56.5 / 53.3 Age range: 35-75 / - / - / -	Patient satisfaction with the type of diversion and assessment of quality of life (social, emotional and physical well being) was made at each interaction with the patient on follow-up and graded as 'Very good', 'Good' or 'Poor'.	Ileal conduit (IC) *versus* Mainz pouch II (MPII) *versus* Ileal neobladder (IN)	Patient satisfaction and QoL	After proper-preoperative counselling and discussion of the advantages and disadvantages of all the three forms of UD patients provided their preferred 1st choice of UD (see Table II). The majority of patients selected ileal neobladder as their first choice UD (60%). However, due to Intra-operative factors (e.g. frozen section analysis) or contraindications only 13.4% of the patients received an Ileal neobladder. *Table II. Patient UD preferences and surgical decisions.* Preferred by patients as 1st choice / Performed by surgeon IC: 3 (10%) / 13 (43.3%) MPII: 3 (10%) / 13 (43.3%) IN: 18 (60%) / 4 (13.4%) Deferred option to surgeon: 6 (20%) Table III reports the patient satisfaction according to UD. The majority of the IC patients thought their diversion was good, the majority of the MPII patients and IN patients thought their diversion was very good. *Table III. Patient satisfaction of UD according to group.* IC (n=13) / MPII (n=13) / IN (n=4) Very Good: 2 (15.4%) / 8 (61.5%) / 3 (75%) Good: 8 (61.5%) / 3 (23.1%) / 1 (25%) Poor: 3 (23.1%) / 2 (15.4%) / -
Design, period	2008					
N	30					
Follow-up	Mean: 27.7 months Range: 3-53 months *3 patients lost to follow-up after attending for one year*					
Funding source	No information provided					

Comments

Selection bias:
- Small sample size

Data collection methods:
- Authors state that a detailed discussion of the objectives and potential complications of radical cystectomy and the advantages/disadvantages of each method of UD was done with the patients before taking for surgery. The patient preference for each specific type of UD was noted.

Integrity of intervention:
- No information on how patient satisfaction data was collected – consultation, questionnaire?
- No information provided on what constituted 'proper pre-operative counselling' and who conducted the discussion.
- No standardised tool used.
- Unclear if the patient preferences were matched – i.e. did the 13.4% of patients receiving an IN select it as their preferred 1st choice?

Statistical analysis:
- No information provided on whether groups differed significantly on any comparisons.

Harano, M. et al. "A pilot study of the assessment of the quality of life, functional results, and complications in patients with an ileal neobladder for invasive bladder cancer" International Journal of Urology (2007): 14: 112-117.

Pub year: 2007		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Japan	Between Sept 1992 and Feb 2003 an orthotopic ileal neobladder reconstruction was performed in 30 consecutive patients. Between Mar 1996 and Sept 2003 ileal conduit or cutaneostomy was performed in 38 consecutive patients. Of the 68 patients 14 (20.6%) had died during the study enrolment. Of the remaining 54, 13 (19.1%) were unreachable via mail resulting in 41 participants enrolled in the study (41/54: 75.9%). As can be seen in Table I there were no statistically significant differences between the two groups on demographic factors. *Table I. demographic data according to UD group.* {table_1}	SF-36 Score range 0-100 Higher scores indicative of a better outcome. For the ileal neobladder patients, a detailed continence questionnaire (not validated) about voiding questions was examined on the same day as the SF-36 survey. Interviewer surveyed the patients.	Ileal neobladder (IN) *versus* Ileal conduit (IC)	HRQOL	No significant difference was apparent in any scale scores between the ileal neobladder and the cutaneous diversion groups (see Table II). *Table II. Average and standard deviation (SD) SF-36 scale scores according to UD group.* {table_2} As shown in Table III complete daytime continence (grades 1 and 2) was achieved in 100% of the ileal neobladder patients and a total of 61.9% of those had complete night-time continence. *Table III. Continence status of the 21 cases with ileal neobladder.* {table_3}
Design, period	Retrospective cohort study 2004					
N	41					
Follow-up	Mean: 44.7 months SD: 20.1 months					
Funding source	No information provided					

	Ileal neobladder (IN)	Cutaneous diversion (CD)
N	21	20
Mean age (SD)	65.7 (6.5)	68.5 (11.2)
Men (%)	21 (100)	17 (85)
Mean follow-up in months (SD)	40.7 (13.7)	49.4 (25.3)
Pathological stage T3 or more (%)	3 (14.3)	5 (25)
Disease free	21 (100)	19 (95)

SF-36 Scales	Ileal neobladder (IN) n=21	Cutaneous diversion (CD) n=20
Physical functioning (SD)	90 (8.3)	79.7 (25.3)
Role-physical functioning (SD)	88.5 (8.3)	80.6 (24.2)
Bodily pain (SD)	72.5 (15)	81.25 (27.7)
General health (SD)	54.3 (10.2)	56 (13.9)
Vitality (SD)	55.8 (9.4)	54.8 (11.5)
Social functioning (SD)	72.9 (5.1)	69.9 (12.4)
Role-emotional functioning (SD)	81.9 (12.2)	72.9 (36)
Mental Health (SD)	60.8 (12.8)	61.8 (11.5)

Grade of continence	Day	Night
Completely dry without pad	19 (90.5)	9 (42.9)
Completely dry with a pad for safety	2 (9.5)	4 (19.0)
No more than one pad per day	0	6 (28.6)
More than one pad per day	0	2 (9.5)

Comments

Selection bias:
- Small sample size
- Analysis of responders and non-responders

Integrity of intervention:
- SF-36 is a general health QoL.

Statistical analysis:
- As a reference, authors indicated the score of the general population data in each aspect of SF-36 scale scores, however, no analysis were conducted because of lack of raw data in the general population. Authors did not give numbers only pictorial representation in the graph.

Shim, B. et al. "Body image following radical cystectomy and ileal neobladder or conduit in Korean patients" Korean Journal of Urology (2014): 51: 161-166.

Pub year: 2014	**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**
Country Korea **Design, period** Retrospective cohort study 2013 **N** 42 **Follow-up** N/a **Funding source** No information provided	Out of 114 patients who underwent radical cystectomy between 2006 and 1012 in a single institution in Korea, 42 were included in the study. 29 in orthotopic ileal neobladder group and 13 in the ileal conduit diversion group. Excluded patients with concomitant medical or psychological disease. As can be seen in Table 1 age was higher in IC group and number of males was higher in IN group. *Table I. demographic data according to UD group.* Ileal neobladder (IN) / Ileal Conduit (IC) N: 29 / 13 Mean age (SD): 63.5 (10.5) / 71.3 (11.5) Men (%): 27 (93) / 5 (38.5) Organ confined stage: 27 (93) / 10 (77) High Grade: 23 (79) / 10 (77) ECOG PS 0-1: 29 (100) / 13 (100)	Body Image Scale (BIS). 10-item measure of affective, behavioural and cognitive dimensions of body image. Score response for each item range 0 to 4. Total score range 0 (no symptoms, distress or concerns with body image) to 30 Interviewer surveyed the patients. Time from surgery to survey was 1.4±1.7yr in the neobladder group and 1.9±1.0yr in the ileal conduit group.	Ileal neobladder (IN) *versus* Ileal conduit (IC)	HRQOL	The groups differed in self-consciousness, dissatisfaction with appearance, difficulty seeing oneself naked, avoidance of people, dissatisfaction with body, dissatisfaction with scarring. Signofocant difference in mean summary score. Patients with orthotopic ileal neobladder had better body image. *Table II. Body image scale* Scale item / Ileal neobladder (IN) n=29 / Ileal Conduit (IC) n=13 Self conscious: 0.17 (0.38) / 1.23 (0.83)* Less physically attractive: 0.34 (0.55) / 0.77 (0.83) Dissatisfied with appearance: 0.17 (0.38) / 0.92 (0.64)* Less masculine/feminine: 0.55 (0.78) / 0.85 (0.90) Difficult to see oneself naked: 0.28 (0.45) / 1.38 (0.87)* Less sexually attractive: 0.72 (0.92) / 0.31 (0.63) Avoid people: 0.12 (0.31) / 0.77 (1.17)* Body less whole: 0.59 (0.78) / 0.46 (0.52) Dissatisfied with body: 0.35 (0.67) / 0.92 (0.86)* Dissatisfied with scar: 0.38 (0.56) / 0.92 (0.86)* **Total score: 3.66 (4.06) / 8.54 (3.56)*** *significant *p* value (<.05)
Comments	*Selection bias:* – Small sample size – No reasons provided for exclusions – Sample size differed between groups *Integrity of intervention:* – BIS only validated in Korean population				

Asgari, M.A. et al. "Quality of life after radical cystectomy for bladder cancer in men with an ileal conduit or continent urinary diversion: A comparative study" Urology Annals (2013): 5: 3: 190-196

Pub year: 2013	**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**

Asgari, M.A. et al. "Quality of life after radical cystectomy for bladder cancer in men with an ileal conduit or continent urinary diversion: A comparative study" Urology Annals (2013): 5: 3: 190-196

Country	Iran	Out of 240 men with MIBC TCC underwent radical cystoprostatectomy. 149 met study criteria. As can be seen in Table I there were no statistically significant differences between the groups on demographic factors. *Table I. demographic data according to UD group.* Ileal Conduit (IC) / Ileal neobladder (IN) / Mainz pouch II (MP) N: 70 / 16 / 63 Mean age (SD): 62.2 (8.6) / 61.9 (9.4) / 61.9 (9.1) pT2 (%): 29 (41) / 6 (38) / 25 (40) pT3: 41 (59) / 10 (63) / 38 (60) G1: 10 (14) / 3 (19) / 10 (16) G2: 36 (51) / 9 (56) / 33 (52) G3: 24 (34) / 4 (25) / 20 (32)	QoL: measure by Kitamura et al (1999) – study included in Somani review No further details of QoL measure	Ileal neobladder (IN) *versus* Ileal conduit (IC) *versus* Mainz Pouch II (MP)	HRQOL	Overall mean score for bathing, sexual desire, desire to void like preoperative status had tendency towards higher values in the patients with bladder substitution. Erectile dysfunction did not differ significantly between groups. *Table II. QoL scores (significant scores only reported)* Scale item / Ileal Conduit (IC) n=70 / Ileal neobladder (IN) n=16 / Mainz pouch II (MP) N=63 Change in way of bathing (much or very much %): 52.9% / 31.2% / 7.9% Use of public bath (much or very much %): 5.7% / 37.5% / 39.7% Decreased sexual desire (much or very much %): 87.1% / 75% / 53.9% Desire to void like pre-operative status (much or very much %): 12.9% / 31.2% / 39.7% Erectile dysfunction: 88.6% / 87.3% / 87.5% High satisfaction with diversion: 12.9% / 19.1% / 12.5% General life satisfaction: 52.8% / 76.2% / 68.7%
Design, period	Prospective cohort study 2005-2010					
N	149					
Follow-up	N/a					
Funding source	None provided					
Comments	*Selection bias:* – Small sample size – Study criteria not reported – Sample size differed between groups *Statistical analysis:* – Only reported significant results					

Asgari, M.A. et al. "Sexual function after non nerve-sparing radical cystoprostatectomy: a comparison between ileal conduit urinary diversion and orthotopic ileal neobladder substitution" International Brazillian Journal of Urology (2013): 39 (4): 474-483

Asgari, M.A. et al. "Sexual function after non nerve-sparing radical cystoprostatectomy: a comparison between ileal conduit urinary diversion and orthotopic ileal neobladder substitution" International Brazillian Journal of Urology (2013): 39 (4): 474-483

Pub year: 2013		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Iran	Out of 206 patients with MIBC TCC who underwent radical cystoprostatectomy, 102 met study criteria. Included: men who were sexually active and potent. 21 lost or violated study criteria. 81 men included in analysis. All bilateral pelvic lymphadenectomy without attempting to spare nerve. Excluded: neurologic or psychiatric disease, relationship problems, chemotherapy or radiotherapy, impaired hepatic and renal function. As can be seen in Table I there were no statistically significant differences between the two groups on demographic factors. *Table I. demographic data according to UD group.* {table_1}	Sexual function: measure by International index of Erectile Function (IIEF) 15 questions assessing five sexual domains. Patients assessed 40wk before surgery, followed-up at 1-, 6- and 12-month after surgery.	Ileal neobladder (IN) *versus* Ileal conduit (IC)	HRQOL – erectile function	Orthotopic ileal neobladder substitutes had more favourable erectile function, and better sexual desire than patients with ileal conduit. *Table II. IIEF scores* {table_2} EF, erectile dysfunction
Design, period	Prospective cohort study 2006-2010					
N	81					
Follow-up	N/a					
Funding source	Not reported					
Comments	*Selection bias:* – Small sample size					

{table_1}

	Ileal Conduit (IC)	Ileal neobladder (IN)
N	41	40
Mean age (SD)	61.4 (9.4)	61.8 (9.6)
pT2 (%)	17(41.5)	15 (38)
pT3	24 (59)	25 (63)
G1	6 (14.6)	6 (15)
G2	21 (51.2)	21 (52.5)
G3	14 (34)	13 (32.5)

{table_2}

Scale item	Ileal Conduit (IC) n=41	Ileal neobladder (IN) n=40
Mean (S.D.) EF score baseline	26.74 (1.12)	26.70 (1.17)
Mean (S.D.) EF score 12 months	5.52 (1.24)	15.60 (1.61)
Completion of intercourse at 12 months n (%)	4 (9.8)	14 (35)
Very low or low sexual desire at 12 months %	51.2	40

Singh, V. et al. "Prospective comparison of quality of life outcomes between ileal conduit urinary diversion and orthotopic neobladder reconstruction after radical cystectomy: a statistical model" BJU International (2013): 113: 726-732.

Pub year: 2013	**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**

Singh, V. et al. "Prospective comparison of quality of life outcomes between ileal conduit urinary diversion and orthotopic neobladder reconstruction after radical cystectomy: a statistical model" BJU International (2013): 113: 726-732.

<table>
<tr><td>Country</td><td>India</td><td rowspan="4">Patients who underwent RC with diversion (IC or ONB) were enrolled.
Excluded those with psychiatric disorder, history of alcohol or substance abuse, cognitive morbidity, or additional oncological disease, or did not have minimum 18 months follow-up data.

Mean patient age was significantly older in IC group. No other baseline differences between groups.

Table I. demographic data according to UD group.
<table><tr><th></th><th>Ileal Conduit (IC)</th><th>Ileal orthotopic neobladder (ONB)</th></tr><tr><td>N</td><td>80</td><td>84</td></tr><tr><td>Mean age (SD)</td><td>58.7 (8.96)</td><td>56.1 (7.26)</td></tr><tr><td>Men (%)</td><td>69 (86)</td><td>74 (88)</td></tr><tr><td>Organ confined stage</td><td>65 (81)</td><td>71 (84.5)</td></tr><tr><td>High Grade</td><td>62 (83)</td><td>62 (76)</td></tr><tr><td>No comorbidity</td><td>34 (42.5)</td><td>37 (44)</td></tr></table>Orthotopic neobladder (ileal n=46; sigmoid n=38)</td><td rowspan="4">EORTC-QLQ C30 [validated Hindi version] self-administered by patients. Completed before surgery, and at 6-, 12-, and 18-month follow-up.
Questions on overall health-related QoL were scored from 1 to 7 (very poor to excellent).</td><td rowspan="4">Orthotopic neobladder (ONB)

versus

Ileal conduit (IC)</td><td rowspan="4">HRQOL</td><td rowspan="4">No pre-operative (baseline) differences between groups. Physical, role, social functioning, and global health status/QoL were rated significantly higher by ONB group at each follow-up. Mean differences in scores from baseline to each follow-up were significantly different between groups, with patients in ONB group performing better postoperatively.

Table II. Mean (SE) differences between EORTC QLQ-C30 scores at baseline and at 12-month follow-up (similar results at 6- and 18-month follow-up)
<table><tr><th>Function Scale item</th><th>Ileal Conduit (IC) n= 80</th><th>Orthotopic neobladder (ONB) n= 84</th></tr><tr><td>Physical</td><td>1.2 (2.0)</td><td>16 (1.7)*</td></tr><tr><td>Role</td><td>-1.2 (2.1)</td><td>11.5 (2.4)*</td></tr><tr><td>Cognitive</td><td>-0.02 (2.8)</td><td>3.2 (2.3)</td></tr><tr><td>Emotional</td><td>1.3 (2.3)</td><td>4 (2.2)</td></tr><tr><td>Social</td><td>2.9 (2.1)</td><td>13.5 (2.3)*</td></tr><tr><td>Global health status/QoL</td><td>17.7 (2)</td><td>37.7 (2.1)*</td></tr><tr><td>Financial difficulty scale</td><td>15.3 (5)</td><td>-18.2 (4.5)*</td></tr></table>*significant p value (<.05)</td></tr>
<tr><td>Design, period</td><td>Prospective cohort study

2007-2012</td></tr>
<tr><td>N</td><td>164</td></tr>
<tr><td>Follow-up</td><td>Mean (SD) 24.27 (6.16) months in IC group and 23.4 (4.97) in ONB group</td></tr>
<tr><td>Funding source</td><td>No information provided</td></tr>
<tr><td>Comments</td><td colspan="6">- Cancer-specific QoL measure used.
- Study was non-randomised</td></tr>
</table>

4.3 Follow up after radical treatment of organ confined muscle-invasive bladder cancer

Review question: What is the optimal follow-up protocol for muscle invasive bladder cancer?

Rationale

Patients previously treated for muscle invasive bladder cancer are at high risk of recurrence. These may occur locally (~20%) and / or, most ominously, as distant metastases (50%). The majority of recurrences are ultimately fatal. The goal of any follow-up protocol is appropriate detection of recurrences such that treatment outcomes may be optimised.

Follow-up protocols should therefore define the type and frequency of tests necessary to diagnose recurrences. These include radiological imaging, urine tests and cystoscopy. There is variation in current follow-up protocols many of which are not evidence based. Patients who have had radical surgery, radical radiotherapy or non-curative treatment may require different follow-up protocols. In addition many patients develop symptomatic recurrences between follow-up visits and several studies have recently shown that there is no difference in overall survival between asymptomatic patients with recurrences found at follow-up and those presenting with symptomatic recurrence.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with MIBC who have : - Received treatment aimed at cure - Not received treatment aimed at cure	Urine tests (Cytology, NMP22, UroVysion, ImmunoCyt) Cystoscopy (Flexi/Rigid) CT scan abdomen and pelvis with plain chest radiograph CT scan chest abdomen and pelvis MRI scan abdomen and pelvis PET scan IVU Renography Blood tests Renal function tests	No follow-up Each other (including frequency and duration of follow-up)	• Local recurrence rate • Overall survival • Disease progression • Distant metastasis free survival • Disease-specific survival • Treatment related complications • Health-related quality of life • Patient experience • Patient preference

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

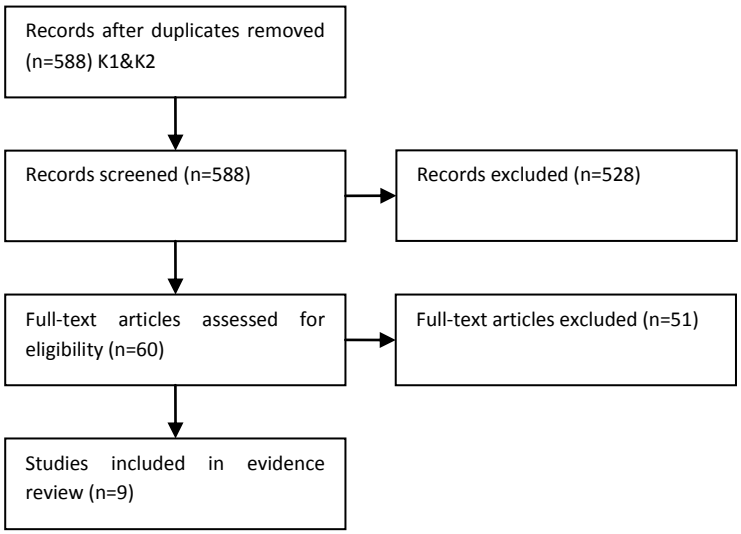
Data synthesis

Evidence was summarised using GRADE. No meta-analysis was possible for this topic.

RESULTS

Result of the literature searches

Figure 71. Study flow diagram



Study quality and results

There was no direct evidence about the optimum follow-up protocol for muscle invasive bladder cancer. Evidence is summarised in Tables 119-120.

Evidence statements

Low quality evidence from eight observational studies including 6,398 patients report overall recurrence rates of between 20% and 46% after radical cystectomy. Most studies report that the risk of both recurrence and metastasis increases with the stage of the primary tumour.

The proportion of asymptomatic recurrences detected by routine follow-up reported in four studies is 12% (Volkmer *et al.*, 2009), 10% (Slaton *et al.*, 1999), 22% (Boorjian *et al.*, 2011) and 34% (Nieuwenhuijzen *et al.*, 2014) indicating that the majority of recurrences are diagnosed through symptom-driven examinations.

One observational study of 574 patients (Perlis *et al.*, 2013) reported a Finnish cohort which received regular urethral washings for cytology compared to a Canadian cohort where routine cytology was

often not performed. There was a trend for urethral recurrences occurring more often in the Finnish cohort (6% vs 2.6%, p=0.06), but no difference in overall survival was reported between patients with urethral recurrence at both sites (very low quality evidence).

One study (Giannarini *et al.*, 2010) reports five-year overall survival of 61.9% (95% CI 57.4-66.7%) and five-year disease-specific survival of 69.8% (95% CI 65.5-74.3%). One study reports that five- and ten-year overall survival is lower in patients with symptomatic recurrence (22% and 10%) than the five- and ten-year overall survival in patients with asymptomatic recurrence (46% and 26%). Patients who were symptomatic at recurrence were at almost 60% increased risk of death than those who were asymptomatic (HR 1.59 (95% CI 1.26 to 2.02) (Boorjian *et al.*, 2011). Similarly, one study reported that patients who were symptomatic at recurrence had shorter survival than those who were asymptomatic (HR 1.58 (p=0.013) (Nieuwenhuijzen *et al.*, 2014).

Very low quality evidence from one observational study of CT urograms reported that findings related to surgery (eg.hydronephrosis, parastomal hernia, urinary tract calculi) were found in 60/105 (57%) of patients during surveillance after radical cystectomy (Shinagare *et al.*, 2013).

Table 119. GRADE evidence profile: Follow-up after radical cystectomy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Follow-up	Control	Relative (95% CI)	Absolute	
Local recurrence rate											
8[1]	observational studies	none	none	none	none	none	972/6796 (14.3%)	NA	-	-	⊕⊕OO LOW
Overall recurrence											
8[2]	observational studies	none	none	none	none	none	2406/6398 (37.6%)	NA	-	-	⊕⊕OO LOW
Overall survival at 5 years post cystectomy											
1[3]	observational studies	none	none	none	none	none	479	-	-	At 5 years 61.9% (57.4 to 66.7%)	⊕⊕OO LOW
Disease-specific survival at 5 years post cystectomy											
1[3]	observational studies	none	none	none	none	none	479	-	-	At 5 years 69.8% (65.5 to 74.3%)	⊕⊕OO LOW
Urethral recurrence (median follow-up 45 months)											
1[4]	observational studies	none	none	none	serious[5]	none	9/151 (6%)	9/352 (2.6%)	RR 2.53 (0.94-5.76)		⊕⊕OO VERY LOW
Upper urinary tract recurrence (median follow-up 45 months)											
1[4]	observational studies	none	none	none	serious[5]	none	8/205 (3.5%)	13/369 (3.5%)	RR 1.11 (0.47-2.63)		⊕⊕OO VERY LOW
Overall survival at 10 years											
1[4]	observational studies	none	none	none	serious[6]	none	205	369		No differences between cohorts (p=0.65)	⊕⊕OO VERY LOW
Distant metastases-free survival											
0	No evidence available										
Treatment-related complications (findings on CTU relating to surgery eg. hydronephrosis, parastomal hernia, urinary tract calculi)											
1[7]	observational studies	none	none	none	serious[5]	none	60/105 (65.7%)	NA	-	-	⊕⊕OO VERY LOW
Health-related quality of life											
0	No evidence available										
Patient experience/preference											
0	No evidence available										

[1] Yafi 2012, Slaton 1999, Giannarini 2010, Kuroda 2002, Volkmer 2009, Boorjian 2011; Perlis 2013; Nieuwenhuijzen 2014; [2] Yafi 2012, Slaton 1999, Giannarini 2010, Kuroda 2002, Volkmer 2009, Boorjian 2011; Shinagare 2013; Nieuwenhuijzen 2014; [3] Giannarini 2010; [4] Perlis 2013 (routine urethral washings for cytology versus no routine urethral washings); [5] Low number of events/wide confidence intervals limits precision
[6] Number of events not reported; [7] Shinagare 2013

Table 120. Recurrence rates reported by included studies

Study	Median follow-up in study	Overall recurrence	Local recurrence	UUT recurrence	Findings related to surgery	Asymptomatic recurrence	Symptomatic recurrence	Overall survival
Yafi 2012	29 months	825/1890 (44%)	208/1890 (11%)					
Volkmer 2009	59 months	444/1270 (35%)	182/1270 (14%)	22/1270 (1.7%)		154/1270 (12%)	290/1270 (23%)	80% of patients with recurrence died within 1 year
Slaton 1999	38 months	97/382 (25%)	27/382 (7%)	9/210 (4.3%)				
Kuroda 2002	64 months	82/330 (25%)	21/330 (6%)	16/330 (4.8%)		28/330 (8.5%)	54/330 (16%)	
Giannarini 2010	4.3 years	174/479 (36%)	12/479 (3%)	14/174 (8%)		87/479 (18%)	87/479 (18%)	5-yr OS rate 61.9%
Boorjian 2011	9.8 years	605/1599 (38%)	450/1599 (28%)			137/1599 (18.6%)	469/1599 (29%)	120/137 (88%) with asymptomatic recurrence died, 439/469 (94%) with symptomatic recurrence died.
Perlis 2013	45 months		18/503 (3.6%)*	21/574 (3.7%)				10 year OS= 43% for UUT recurrence, 66% for urethral recurrence and 68% for no recurrence
Nieuwenhuijzen 2014	64 months	158/343 (46%)	54/343 (16%)			54/158 (34%)	101/158 (64%)	5-yr OS =46%; 5-yr DSS=53%. Survival shorter for symptomatic recurrences than asymptomatic recurrences.
Shinagare 2013	63 months	21/105 (20%)		3/105 (2.9%)	60/105 (57%)			
Total		**2406/6398 (37.6%)**	**972/6796 (14.3%)**	**85/2366 (3.6%)**	**60/105 (57%)**	**460/3836 (12%)**	**1001/3836 (26%)**	

*Urethral recurrences

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Reason: relevant to another topic (follow-up for NMIBC)

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Evidence tables

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
Yafi 2012 Canada	Retrospective review 1998-2008	1890 who had undergone RC	Median age 68 (range 26-90) 91% pelvic lymphadenectomy, 28% adjuvant chemotherapy.	Complete blood counts, serum chemistries, abdominal imaging, chest radiography every 3-6mo for at least 3 yrs. Bone scans ordered when clinically indicated.	NA	Median 29 mo (1-176)	**Recurrence:** 825/1890 (43.6%) had recurrence with a median time to recurrence 10.1 (1-192) mo. 90 and 97% of recurrences occurred 2 and 5 yrs after RC. 29% within first 6mo. 48.6% distant recurrence (42% lung, 36% bone, 27% liver, 2% brain), (208/1890, 11% overall) 25.2% pelvic, 14.5% retroperitoneal, 11.8% multiple regions. Of those who had a recurrence 250 (30%) received salvage therapy (140 and 110 received systemic chemo and RT) 5yr RFS: 25% pTxN+; 44% ≥pT3N0; 66% ≤pT2N0 Median time to recurrence: 9mo (1-72) pTxN+; 10mo (1-70) ≥pT3N0; 14mo (1-192) ≤pT2N0	NA	Authors recommend a stage specific approach to surveillance after RC
Volkmer 2009 Germany	Retrospective review 1986-2006	1270 who had undergone RC with PLN	Median age at RC 63.8 yrs (range 23-91) 1031 (81%) male, 239 (19%) female. 20.9% superficial BC, 31.4% organ confined, 22.5% non-organ confined, 25.1% lymph node positive. 93% TCC, 3.6% squamous cell. 65% had ileal neobladder for urinary diversion	F/up recommended for 5yrs. 3monthly clinical examination. US of abdomen, chest x-ray, CT of abdomen every 6mo, bone scan and IVP every 12 mo. Additional symptom driven imaging as necessary.		Median 59mo (0-271)	**Recurrence:** 444/1270 (35%). 154 (12%) recurrences detected by patients in asymptomatic state by imaging during regular follow-up examinations at a mean of 20mo after RC. 290 (23%) recurrences were detected by symptom driven exams, at a mean of 17.5mo after RC. Overall probability of recurrence at 1-yr 23%, 5-yr 38%; 10-yr 45%; 20-yr 49%. Half of tumour recurrences were detected at 9mo for local recurrence and 13mo for distant mets. 0.1% recurrence in UUT, 1.7% recurrence in urethra. **Survival:** With tumour recurrence 80% died within 1yr and only 3.5% survived >5yrs.	NA	No survival advantage in those with asymptomatic versus symptomatic recurrences.
Slaton 1999 USA	Retrospective review 1985-1994	382 who had undergone RC	N0 (n=319), N1-2 (n=63). All M0 TCC	Chest x-ray, CT of abdomen and pelvis, liver function tests,	NA	Median 38 months (1-138)	**Recurrence:** 97/382 (25%) developed metastases, a median of 12 mo (1-100) after RC (33 lung, 27 pelvis, 19 bone, 18 liver, 10	NA	Authors recommend a stage specific

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
				alkaline phosphatase tests every 3-4mo for 2 yrs, then every 6mo for 2 yrs, then annually. Most patients underwent routine CT depending on surgeon preference.			retroperitoneal lymph nodes, 4 supradiaphragmatic lymph node, 2 skin, 1 brain, 1 pancreas). 10/97 (10%) of recurrences were detected by routine CT without symptoms, abnormal serum chemistry or disease recurrence at another site. 4/78 (5%) pT1, 28/141 (20%) pT2, 65/163 (40%) pT3 or higher. Within 36mo, recurrence was noted in 22/28 (79%) pT2 and 61/65 (94%) pT3. 4/210 urethral recurrences were found after a median f/up of 15mo (range 3-45). 9 patients had ureteral recurrence at a median of 25mo after RC – 5 of these were identified on surveillance studies of the UT, including 4 excretory urograms and 1 loopogram.		approach to surveillance after RC
Kuroda 2002 Japan	Retrospective review 1979-1999	330 who underwent curative RC	Mean age 64 years (range 33-97) 273 (83%) male, 57 (17%) female	Chest x-ray, multichannel blood tests, urine cytology every 3mo for 2 yrs, then every 6mo for 3 yrs, and once a year thereafter. Most patients CT scan every 4mo for 2 yrs, then every 6-12 mo for 3 yrs	NA	Median 64 mo (2-250)	**Recurrence:** 82/330 (25%) developed metastases at a median of 8 months (1-186) after RC. 103 metastatic lesions – 29 bone, 24 lung, 21 pelvic, 18 distant lymph node, 10 liver, 1 skin Recurrence: 10/124 (8%) pT1 or lower, 17/101 (17%) pT2, 55/101 (54%) pT3 or higher. 86% of patients with bone mets were symptomatic, 58% of lung mets had no symptoms. 54/82 patients with mets were initially symptomatic. Most asymptomatic mets were identified with chest x-ray, abdominal CT or US. All asymptomatic lung mets were identified by chest x-ray and most asymptomatic liver and lymph node mets by abdominal CT scan. 3/169 (1.8%) urethral recurrences were identified at a median of 53 mo (2-250) – all symptomatic 16 (4.8%) developed UUT recurrence at a median of 30 mo (8-129) after RC. 12/16 (75%)		Authors recommend a stage specific approach to surveillance after RC

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							were identified by surveillance – 7 excretory urography, 4 cytology, 1 ultrasonography. 19 patients with UUT complications – 16 identified by surveillance (excretory urography and ultrasonography), other 3 were symptomatic.		
Giannarini 2010 Switzerland	Retrospective review 1985-2009	479 undergone RC and extended PLND with ileal orthotopic bladder substitution for primary TCC. Excluded neoadjuvant CT or RT, salvage RC, irregular follow-up	Median age: 65.7 Male: 439 (91.6) Female: 40 (8.4) Nerve-sparing technique None: 80 (17) Unilateral: 301 (63) bilateral: 98 (21) Tumour stage/grade Ta/Tis: 11 (2.3) T1: 100 (23) T2: 181 (38) T3: 156 (33) T4: 31 (6.5) G1: 2 (0.4) G2: 21 (4.4) G3: 456 (95) N0: 366 (76) N+: 113 (24) Adjuvant CT: 42 (8.7) Type of follow-up scheme Original: 227 (47) Revised: 252 (53)	Original prospective follow-up scheme replaced in 1999 by a risk-oriented protocol. Physical exam, blood tests every 3 mo in 1st year, then every 6mo until 5 years, then annually, chest xray (up to yr5), bone scan and CT scan only if ≥pT3 or T1-4 N+ (at 6 and 12 mo), IVU with tomography annually until 5 yr. Patients with symptoms immediately evaluated by appropriate imaging	NA	Median 4.3 years (range 0.3-20.9)	**Recurrence:** 174/479 (36.3%) had recurrence. 87 diagnosed at routine follow-up and 87 by symptoms. Median time between RC and recurrence 0.9 yrs. 90% of recurrences were diagnosed within the first 3 years after RC. 12 pelvic, 106 distant metastases (38 bone, 36 lung), 18 concomitant pelvic and distant recurrence. 38/174 (21.8%) had secondary urothelial tumour. 14 (8%) in the UUT and 24 (13.8%) urethra. 79% secondary urothelial tumours detected by routine surveillance – 88% cytology **Survival:** 5-yr cancer-specific survival rate 69.8% (95% CI 65.5-74.3%) 5-yr OS rate 61.9% (95% CI 57.4-66.7%). 144/174 recurrent patients died from bladder cancer, 8 died from other causes.	NA	Patients with recurrences detected at routine follow-up had slightly higher survival than patients with symptomatic recurrences. HR for CSS 0.65 (0.46-0.91), OS 0.66 (0.48-0.92)
Boorjian 2011 USA	Retrospective review 1980-2000	1599 who underwent RC for non metastatic BC	Asympt / Sympt Male: 121 (88) / 366 (78) Female: 16 (12) / 103 (22) pTa/T1/CIS: 46 (33) / 99 (21) pT2: 43 (31) / 143 (31) pT3/4: 48 (35) / 227 (48) pN0: 95 (69) / 316 (67) pN+: 20 (15) / 95 (20) pNx: 22 (16) / 58 (12) Adjuvant or neo CT	Every 3mo for first 2 yrs, every 6mo for next 2 yrs, then annually in patients without recurrent disease. Physical exam, cytology, imaging chest/abdomen/pelvis. Most patients had CT, CT urogram or excretory	NA	Median 9.8 years (0-30)	**Recurrence:** 606/1599 (37.3%) recurrence. 137/606 (22.6%) with recurrence were asymptomatic (median 1.3 yrs after RC), 469/606 (77.4%) detected by symptom driven examinations (e.g. pain and haematuria) (median 1 yr after RC). 450 abdomen/pelvis, 185 bone, 176 thorax, 39 brain, 154 secondary urothelial tumours. Almost all patients with recurrence in brain, bone, abdomen/pelvis or thorax were symptomatic,	NA	Patients who were symptomatic at recurrence were at almost 60% increased risk of death than those who were asymptomatic (HR 1.59 (1.26-

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			Yes 12 (9) 42 (9)	urogram, combined with chest xray or chest CT. Bone scan and brain imaging done as clinically indication			61% of patients with recurrent urothelial tumour were symptomatic **Survival:** 120/137 (88%) with asymptomatic recurrence died, 439/469 (94%) with symptomatic recurrence died. 5-and 10-year OS in patients with symptomatic recurrence = 22% and 10% 5-and 10-year OS in patients with asymptomatic recurrence =46% and 26%		2.02)
Perlis 2013 Canada and Finland	Retrospective cohort study 1986-2005 Finland, 1992-2008 Canada	N=574 patients undergoing RC and LN for urothelial bladder cancer. Salvage RC and neoadjuvant chemo excluded.	N (%) female 127 (22) male 447 (78) Median age 68 (32-88) Finland 205 (36) Canada 369 (64) P stage pT0-T1 215 (37) pT2 119 (21) pT3 169 (29) pT4 71 (12) LN+ 114 (20) LN- 330 (57) Concomitant CIS 244 (43) LVI 204 (36) Urethral recurrence 18/503 (4) UUT recurrence 21 (4)	Every 3 months for first year, bi-annually until year 5 and annually thereafter. In Finland: urine cytology and urethral washings for cytology every 6 mo. Contrast enhanced abdominal and pelvic CT at 6mo. Further imaging if symptoms or clinical concern. Follow-up in Toronto was surgeon dependant and often did not consist of routine follow-up.	Recurrence rate compared between 2 centres – Finland and Canada	Median 45 months	**Upper urinary tract (UUT) recurrence:** 21/574 (3.7%). Rates were similar between Finland (8/205) and Canada (12/369) **Urethral recurrence (excluding 71 patients who had urethrectomy during RC):** 18/503 (3.7%), trend towards becoming more common in Finland (9/151, 6%) than Canada (9/352, 2.6%) No difference in time to UUTR or UR between sites. **Overall survival** 10 years 43% for patients with UUT recurrence, 66% for those with UR recurrence and 68% for patients without recurrence. OS did not differ between the two centres or by type of recurrence.	NR	Not reported how the follow-up protocols from the two institutions differed. Canada cohort had more advanced disease (LN+, stage T2 or higher, concomitant CIS)
Shinagare 2013 USA	Retrospective cohort study 200-2011	N=105 patients having CT urogram during follow-up after RC for bladder cancer	79 male, 26 female. Mean age 65 (range 43-85)y Median time between RC and CTU 39 months (0-229)	CTU using 4-, 16- or 64-detector CT scanners. Single bolus 3-phase protocol used (unenhanced scan of abdomen and pelvis, nephrographic scan phase of kidneys after	n/a	Median 63 months (range 1-234)	225 CTUs were performed in 105 patients. **Findings related to surgery:** 60/105 (57%). Of 60 patients with findings relating to complications from surgery, 5 (8.3%) required surgery. **Locoregional or distant recurrence of bladder cancer:** 21 (20%) Visceral mets 16 (15.2%), lymph node metastases 13 (12.4%), pelvic recurrence 1 (1%).	NR	Unclear how patients were selected – potential selection bias. Unclear if CTU was performed routine.

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>i.v. injection, excretory phase scan of abdomen and pelvis 15min after contrast medium injection.</td><td></td><td></td><td>Of 21 patients, 7 had coexisting nodal and distant mets and one had local recurrence with nodal and distant mets.
UUT recurrence: 3/105 (2.9%)
Findings suggestive of UTT were seen in 11 (10.5%). Of these, 7 were false positive, 3 were true positive, and one was lost to follow-up.
UUT developed after a median of 43 months (range 16-73) months from surgery.</td><td></td><td></td></tr>
<tr><td>Nieuwenhuijzen 2014
Netherlands</td><td>Retrospective review
1990-2006</td><td>343 consecutive patients treated with RC.
47 salvage RC after previous RT with curative intent for bladder cancer</td><td><table><tr><td></td><td>N (%)</td></tr><tr><td>female</td><td>87 (25)</td></tr><tr><td>male</td><td>256 (75)</td></tr><tr><td>Median age</td><td>62.3</td></tr><tr><td>P stage</td><td></td></tr><tr><td>pT1/Ta/Tis</td><td>41 (12)</td></tr><tr><td>pT2</td><td>137 (40</td></tr><tr><td>pT3</td><td>97 (28)</td></tr><tr><td>pT4a</td><td>43 (13)</td></tr><tr><td>pT4b</td><td>25 (7)</td></tr><tr><td>LN+</td><td>116 (34)</td></tr><tr><td>LN-</td><td>227 (67)</td></tr><tr><td>Concomitant CIS</td><td>86 (25)</td></tr><tr><td>Neoadjuvant chemo</td><td>N=69</td></tr><tr><td>Adjuvant chemo</td><td>N=13</td></tr></table></td><td>Follow-up 3-4 months intervals in first year, semi-annually the next two years and annually thereafter, or more frequent if clinically indicated.
Included physical exams, routine serum chemistry, radiographic examination by pelvic-abdominal CT scan and chest x-ray, cystoscopy when neobladder used, and cytological exam of urine. Bone scans on indication. 97% had follow-up exceeding 1yr</td><td>n/a</td><td>Median 64 months (2-196 mo)</td><td>Overall survival 176 (51%) died after median follow-up exceeding 5yrs. 5-yr OS =46%
Disease-specific survival 134 (39%) died of disease. 5-yr DSS= 53%
Recurrence 158 (46%) had recurrence; 104 (30%) distant mets; 33 (10%) local pelvic tumour recurrence; 21 (6%) concomitant distant mets with pelvic recurrence; 5 urethral recurrence.

Median time to any tumour recurrence= 8.7 months. 84% of all recurrence detected within 2yrs.

Of all recurrences, 64% were symptomatic, 34% were diagnosed at standard follow-up. 2% diagnosed coincidentally (e.g. autopsy)
Survival after symptomatic recurrence was shorter compared to asymptomatic recurrence in univariate analysis (HR 1.58, p=0.013) and multivariate analysis (HR 2.40, 95% CI 1.61-3.58, p=0.013)</td><td>No conflicts of interest declared</td><td></td></tr>
</table>

5 Managing locally advanced or metastatic bladder cancer

5.1 Managing patients with distant metastases

5.1.1 First line chemotherapy

Review question: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

Rationale

Most patients who die of bladder cancer will do so with metastatic disease. The main treatment used to prolong life and palliate/alleviate the symptoms is chemotherapy. Most studies report benefits in terms of response, symptom control and survival but this comes at the cost of significant treatment related toxicity. Though there are anecdotal reports of long term survivors these seem to be rare. Most clinicians use cisplatin based multiagent chemotherapy that is suitable for patients with normal renal function and good performance status. What evidence if there that the gains out way the toxicity? Does the treatment need to be cisplatin based or can less intensive therapy be used? Gemcitabine Cisplatin (GC) is widely used but is this best schedule in comparison to other schedules such as MVAC, CMV or accelerated MVAC. Does adding paclitaxel (GCP) improve results? Are there any other additional therapies that can be recommended? Carboplatin has a better toxicity profile (less sickness, fatigue, neuropathy but more myelosuppression) than cisplatin but there are concerns that carboplatin schedules such as gemcitabine carboplatin or carboplatin/methotrexate/vinblastine are less active. Does the evidence support this view leaving cisplatin based schedules as the treatment of choice despite their added toxicity? Most commonly 6 cycles of chemotherapy are used. Is there evidence that more or less chemotherapy than this would be suitable?

Many patients are elderly and/or have impaired performance status and/or impaired renal (kidney) function. In these patients there have been questions as to whether patients benefit from chemotherapy. Is the evidence that chemotherapy improves outcomes compared to best supportive care? If so what is the preferred schedule? Should carboplatin based treatment be used? Should some patients be treated with split dose cisplatin schedules? Are there are 'platinum free' schedules that are suitable? Are there groups or sub groups of patients that should/should not be treated?

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with incurable locally advanced or metastatic bladder cancer Cisplatin fit (GFR >60 PS 0/1)	Chemotherapy agents for first-line chemotherapy (alone or in combination): Methotrexate, Vinblastine, Adriamycin, Cisplatin, Gemcitabine, Carboplatin, Paclitaxel, Docetaxel	Each other (Cisplatin vs Non Cisplatin) No treatment	• Overall survival • Progression free survival • Treatment-related mortality • Treatment related morbidity • Health-related quality of life, inc patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. Randomised trials were selected for this review question.

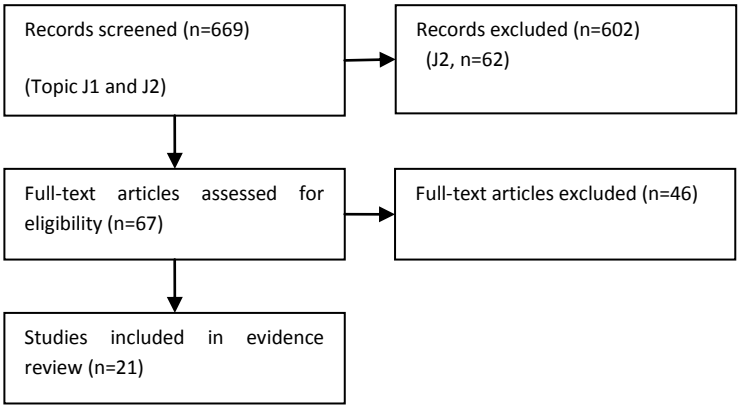
Data synthesis

Data was extracted into RevMan and risk ratios were calculated when possible. Data from one systematic review of cisplatin versus non-cisplatin based chemotherapy was reported. Consideration was given to trials including patients eligible and not eligible for cisplatin-based chemotherapy.

RESULTS

Result of the literature searches

Figure 72. Study flow diagram



Study quality and results

Evidence was identified from 21 randomised trials and is summarised in Tables 121-135.

Evidence statements

Cisplatin-based chemotherapy

One phase II trial (Hillcoat et al., 1989) of 108 participants provided low quality evidence that there was no difference in overall survival between those treated with single agent Cisplatin (C) therapy or a combination of Cisplatin and Methotrexate (CM). Time to progression was longer with CM, but this difference was only significant during the first 12 months of therapy. Toxicity was greater in the CM arm, including haematological toxicity (26% vs. 7%) and mucositis (19% vs. 0%). Single agent Cisplatin was also compared to MVAC in one trial of 246 participants (Loehrer et al., 1992). Overall survival and progression-free survival were greater for MVAC than Cisplatin alone (low quality evidence). At 6-year follow-up, MVAC still showed a survival advantage over Cisplatin (Saxman et al., 1997). However,

combined MVAC was more toxic than Cisplatin, with increased rates of grade 3-4 leukopenia, granulocytopenic fever, and mucositis. There were no differences in treatment-related mortality (4% vs. 0%). There was no evidence about health-related quality of life.

One trial (220 participants) of moderate quality reported increased duration of overall survival (14.2 months vs. 9.3 months) and time-to-progression (9.4 months vs. 6.1 months) with MVAC and granulocyte colony-stimulating factor (GCSF) compared to Docetaxel and Cisplatin with GCSF (Bamias et al., 2004). There were no differences in rates of grade 3-4 thrombocytopenia or anaemia. Neutropenia (36% vs. 19%) and neutropenic sepsis were more common in the MVAC arm. There were no differences in treatment-related mortality. One moderate quality trial (263 participants) compared high-dose intensity MVAC and GCSF (HD-MVAC) with classic MVAC (Sternberg et al., 2001/2006). After a median of 7.3 years follow-up, HD-MVAC produced a small improvement in risk of death and risk of progression. There were lower rates of whole blood cell toxicity and neutropenic fever with HD-MVAC, with no differences between arms for thrombocytopenia, mucositis and treatment-related mortality. Health-related quality of life was not reported.

One phase III trial (405 participants) of MVAC versus Gemcitabine and Cisplatin (GC) providing high quality evidence reported no differences in overall survival and progression-free survival between trial arms (von der Maase et al., 2000/2005). Rates of grade 3-4 anaemia and thrombocytopenia were greater in the GC arm, whereas neutropenia and neutropenic sepsis were more common in the MVAC arm. Mean quality of life scores were not reported but the authors state that quality of life (as measured by the EORTC QLQ C30) was maintained on both arms throughout the study with improvements in emotional functioning and pain. One observational study, where oncology professionals were interviewed as patient representatives, provided very low quality evidence that respondents were more likely to choose GC over MVAC for a reduced incidence of neutropenic sepsis, mucositis, or serious weight loss. Respondents were more willing to accept GC over MVAC even when a hypothetical life expectancy was reduced from 60 weeks to 45 weeks.

One randomised phase III trial (130 patients) of dose dense MVAC versus dose dense GC provided low quality evidence of no difference in overall survival or progression-free survival between groups. Grade 3-5 toxicities were reported in 50% of the DD-MVAC group and 44% of the DD-GC group. Two toxicity-related deaths were both in the DD-MVAC arm due to non-neutropenic sepsis (Bamias et al., 2013).

GC was compared with Pacitaxel, Gemcitabine and Cisplatin (PCG) in one randomised phase II trial of 85 patients (Lorusso et al., 2005) and one randomised phase III trial of 626 participants (Bellmunt et al., 2012). The phase III trial provided high quality evidence of no difference in overall survival and progression-free survival between trial arms. However, there was a small effect in the subgroup of patients with primary bladder tumours, with longer overall survival in patients treated with PCG (15.9 vs. 11.9 months, HR 0.80, 0.66 to 0.97). Grade 3-4 thrombocytopenia was more common in the GC arm, and grade 3-4 neutropenia was more common in the PCG arm (64% vs. 51%). Health-related quality of life was not reported.

Cisplatin-based versus carboplatin-based chemotherapy

Bellmunt et al. (1997) provided low quality evidence, comparing MVAC with methotrexate, carboplatin and vinblastine (M-CAVI) in 47 patients. Median disease-related survival was greater in the MVAC arm (hazard ratios were not reported). There were no differences in toxicity between arms. The study was

terminated early and failed to reach accrual target. One underpowered trial (84 participants), which was closed early for slow accrual provided very low quality evidence comparing MVAC with carboplatin and paclitaxcel (CaP) (Dreicer et al., 2004). There were no differences between arms for overall survival and progression-free survival. Rates of neutropenia and anaemia were higher in the MVAC arm, but there were no differences in rates of thrombocytopenia and treatment-related mortality. It was reported that there were no differences in quality of life over time by treatment arm, but low numbers of participants were assessed for quality of life, which limits the precision of this outcome. One underpowered trial (110 participants) provided very low quality evidence of no difference in overall survival, time-to-progression, and toxicity between patients treated with Gemcitabine and Cisplatin versus Gemcitabine and Carboplatin (Dogliotti et al., 2007).

Four trials comparing cisplatin-based chemotherapy with carboplatin-based chemotherapy were included in the meta-analysis by Galsky et al. (2012). Very low quality evidence from two studies showed no difference in survival rate at 12 months (RR 0.76, 95% CI 0.56 to 1.07). Progression-free survival was not reported consistently across studies and could not be pooled in a meta-analysis. Therefore, overall tumour response rates and complete tumour response rates were pooled and risk ratios (95% CIs) were calculated. A partial tumour response was defined as a 50% reduction in bidimensional tumour measurements and a complete response as a resolution of radiographic abnormalities. A majority of patients had a performance status of 0 to 1 with adequate renal function. The meta-analysis demonstrated a higher likelihood of achieving an overall response (RR 1.34, 95% CI 1.04 to 1.71) and a complete response (RR 3.54, 95% CI 1.48 to 8.49) with cisplatin-based chemotherapy. However, this analysis is based on three small phase II studies and one phase III trial which was closed early due to poor accrual. The chemotherapy agents used and the doses of carboplatin used differed across studies.

Chemotherapy in 'unfit' patients

Moderate quality evidence for overall survival and progression-free survival was provided by one phase III RCT (238 participants) comparing Gemcitabine & Carboplatin (GCarbo) with Methotrexate & Carboplatin & Vinblastine (M-CAVI) (De Santis et al., 2012) in patients unfit for cisplatin-based therapy. After a median of 4.5 years follow-up there were no differences in overall survival (HR 0.94, 0.72 to 1.02) and progression-free survival (HR 1.04, 0.8 to 1.35) between the two treatments. GCarbo produced a lower rate of severe acute toxicity than M-CAVI (9% vs. 21%). There were no differences between treatments for changes in health-related quality of life from baseline to end of cycle 2, although mean scores were not reported and there was less than 50% response rate after the baseline assessment.

Table 121. GRADE evidence profile: Cisplatin & Methotrexate (CM) versus Cisplatin (C)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CM	C	Relative (95% CI)	Absolute	
Overall survival (follow-up range 2-5 years)											
1[1]	randomised trials	none	none	none	very serious[2]	none	N=53	N=55	HR not reported	Median OS, 8.7 months vs. 7.2 months[3]	⊕⊕OO LOW
Progression-free survival (follow-up 2-5 years)											
1[1]	randomised trials	none	none	none	very serious[2]	none	N=53	N=55	HR not reported	Median PFS, 5 months vs. 2.8 months[4]	⊕⊕OO LOW
Toxicity - Grade 3-4 Haematological											
1	randomised trials	none	none	none	very serious[2]	none	14/53 (26.4%)	4/55 (7.3%)	RR 3.63 (1.28 to 10.33)	191 more per 1000 (from 20 more to 679 more)	⊕⊕OO LOW
Toxicity - Grade 3-4 Mucositis											
1[1]	randomised trials	none	none	none	very serious[5]	none	10/53 (18.9%)	0/55 (0%)	RR 21.78 (1.31 to 362.56)	-	⊕⊕OO LOW
Toxicity - Grade 3-4 Nausea/Vomiting											
1[1]	randomised trials	none	none	none	very serious[5]	none	23/53 (43.4%)	14/55 (25.5%)	RR 1.70 (0.99 to 2.95)	178 more per 1000 (from 3 fewer to 496 more)	⊕⊕OO LOW
Treatment-related mortality											
1[1]	randomised trials	none	none	none	very serious[5]	none	2/53 (3.8%)	1/55 (1.8%)[6]	RR 2.08 (0.19 to 22.22)	20 more per 1000 (from 15 fewer to 386 more)	⊕⊕OO LOW
Health-related quality of life											
0	no evidence available										

[1] Hillcoat (1989); [2] Small sample size/low number of events limit precision of this outcome; [3] Median overall survival was 8.7 months with CM, and 7.2 months with C (p=0.7). Number of events in each arm during follow-up was not reported. Hazard ratios were not reported; [4] Median time-to-progression was 5 months with CM, and 2.8 months with C (the log rank test was not significant, p=0.13, but the Wilcoxon test was significant, p=0.02). Hazard ratios not reported. By the end of the second year after randomisation 10% of patients in both arms remained progression free (no significant differences between arms); [5] Wide confidence intervals/low number of events limits the precision of this outcome; [6] One death on the C arm resulted from neutropenic sepsis following M therapy given after C treatment

Table 122. GRADE evidence profile: MVAC (Methotrexate, Vinblastine, Doxorubicin & Cisplatin) versus Methotrexate & Cisplatin (MC)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MVAC	MC	Relative (95% CI)	Absolute	
Overall survival											
0	no evidence available										
Progression-free survival											
0	no evidence available										
Toxicity - Grade 3-4 Leucopoenia											
1[1]	randomised trials	none	none	none	very serious[2]	none	2/14 (14.3%)	1/14 (7.1%)	RR 2.00 (0.20 to 19.62)	71 more per 1000 (from 57 fewer to 1000 more)	⊕⊕OO LOW
Toxicity - Grade 2-3 Thrombocytopenia (WHO criteria)											
1[1]	randomised trials	none	none	none	very serious[2]	none	2/14 (14.3%)	1/14 (7.1%)	RR 2.00 (0.2 to 19.62)	71 more per 1000 (from 57 fewer to 1000 more)	⊕⊕OO LOW
Toxicity - Anaemia (Hb loss >3g)											
1[1]	randomised trials	none	none	none	very serious[2]	none	1/14 (7.1%)	1/14 (7.1%)	RR 1.00 (0.07 to 14.45)	0 fewer per 1000 (from 66 fewer to 961 more)	⊕⊕OO LOW
Treatment-related mortality											
0	no evidence available										
Health-related quality of life											
0	no evidence available										

[1] Pizzocaro (1991); [2] Small number of participants/events and wide confidence intervals reduces the precision of this outcome

Table 123. GRADE evidence profile: CMV (Cisplatin, Methotrexate & Vinblastine) versus MV

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CMV	MV	Relative (95% CI)	Absolute	
Overall survival (mortality rate, maximum follow-up 2 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	101/108 (93.5%)	103/106 (97.2%)	HR 0.68 (0.51 to 0.9)	Median OS, 7 vs. 4.5 mo	⊕⊕⊕O MODERATE
Progression-free survival (progression or death rate, maximum follow-up 2 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	104/108 (96.3%)	104/106 (98.1%)	HR 0.55 (0.41 to 0.73)	Median PFS, 5.5 vs. 3 mo	⊕⊕⊕O MODERATE
Toxicity - Grade 3 leucopoenia or thrombocytopenia											
1[1]	randomised trials	none	none	none	serious[2]	none	5/108 (4.6%)	0/106 (0%)	RR 10.8 (0.6 to 192.89)	-	⊕⊕⊕O MODERATE
Toxicity - Neutropenic fever requiring hospital admission and i.v antibiotics											
1[1]	randomised trials	none	none	none	serious[2]	none	11/108 (10.2%)	2/106 (1.9%)	RR 5.40 (1.23 to 23.78)	83 more per 1000 (from 4 more to 430 more)	⊕⊕⊕O MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	none	serious[2]	none	5/108 (4.6%)	0/106 (0%)	RR 10.80 (0.6 to 192.89)	-	⊕⊕⊕O MODERATE
Health-related quality of life											
0	no evidence available										

[1] Mead (1998); [2] Wide confidence intervals /low number of events limit the precision of this outcome

Table 124. GRADE evidence profile: MVAC (Methotrexate, Vinblastine, Doxorubicin & Cisplatin) versus Cisplatin

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MVAC	Cisplatin	Relative (95% CI)	Absolute	
Overall survival (mortality rate, median follow-up 19.7 months)											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	106/126 (84.1%)	115/120 (95.8%)	HR 0.61 (0.47 to 0.79)	Median OS, 12.5 vs. 8.2 mo	⊕⊕OO LOW
Progression-free survival (progression or death rate, median follow-up 19.7 months)											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	108/126 (85.7%)	113/120 (94.2%)	Unable to calculate HR	Median PFS, 10 vs. 4.3 mo	⊕⊕OO LOW
Toxicity - Grade 3-4 Anaemia											
1[1]	randomised trials	none	none	none	very serious[3]	none	1/126 (0.8%)	1/120 (0.8%)	RR 0.95 (0.06 to 15.06)	0 fewer per 1000 (from 8 fewer to 117 more)	⊕⊕OO LOW
Toxicity - Grade 3-4 Leucopoenia											
1[1]	randomised trials	none	none	none	very serious[3]	none	30/126 (23.8%)	1/120 (0.8%)	RR 28.57 (3.96 to 206.24)	230 more per 1000 (from 25 more to 1000 more)	⊕⊕OO LOW
Toxicity - Grade 3-4 Granulocytopenic fever											
1[1]	randomised trials	none	none	none	very serious[3]	none	13/126 (10.3%)	0/120 (0%)	RR 25.72 (1.55 to 427.99)	-	⊕⊕OO LOW
Toxicity - Grade 3-4 Mucositis											
1[1]	randomised trials	none	none	none	very serious[3]	none	21/126 (16.7%)	0/120 (0%)	RR 40.97 (2.51 to 668.86)	-	⊕⊕OO LOW
Treatment-related mortality											
1[1]	randomised trials	none	none	none	very serious[3]	none	5/126 (4%)	0/120 (0%)	RR 10.48 (0.59 to 187.51)	-	⊕⊕OO LOW
Health-related quality of life											
0	no evidence available										

[1] Loehrer (1992) / Saxman (1997); [2]Number of participants ineligible for the study and included in the final analysis differ between reports by Loehrer (1992) and Saxman (1997). HR calculated from p-value and number of observed events reported in Loehrer (1992); [3] Wide confidence intervals and/or low number of events limit the precision of this outcome

Table 125. GRADE evidence profile: High-dose MVAC versus MVAC

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose MVAC	MVAC	Relative (95% CI)	Absolute	
Overall survival (mortality rate, median follow-up 7.3 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	101/134 (75.4%)	112/129 (86.8%)	HR 0.76 (0.58 to 0.99)[3]	Median OS, 15.1 vs. 14.9 mo	⊕⊕⊕O MODERATE
Progression-free survival (progression or death rate, median follow-up 7.3 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	109/134 (81.3%)	116/129 (89.9%)	HR 0.73 (0.56 to 0.95)[4]	Median PFS, 9.5 vs. 8.1 mo	⊕⊕⊕O MODERATE
Toxicity - Grade 3-4 Whole blood cell (WBC) (WHO criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	27/134 (20.1%)	80/129 (62%)	RR 0.32 (0.23 to 0.47)	422 fewer per 1000 (from 329 fewer to 478 fewer)	⊕⊕⊕O MODERATE
Toxicity - Grade 3-4 Thrombocytopenia (WHO criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	28/134 (20.9%)	22/129 (17.1%)	RR 1.23 (0.74 to 2.03)	39 more per 1000 (from 44 fewer to 176 more)	⊕⊕⊕O MODERATE
Toxicity - Grade 3-4 Mucositis (WHO criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	13/134 (9.7%)	22/129 (17.1%)	RR 0.57 (0.3 to 1.08)	73 fewer per 1000 (from 119 fewer to 14 more)	⊕⊕⊕O MODERATE
Neutropenic fever											
1[1]	randomised trials	none	none	none	serious[2]	none	13/134 (9.7%)	33/129 (25.6%)	RR 0.38 (0.21 to 0.69)	159 fewer per 1000 (from 79 fewer to 202 fewer)	⊕⊕⊕O MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	none	serious[2]	none	1/134 (0.7%)	1/129 (0.8%)	RR 0.96 (0.06 to 15.23)	0 fewer per 1000 (from 7 fewer to 110 more)	⊕⊕⊕O MODERATE
Health-related quality of life											
0	no evidence available										

[1] Sternberg (2001/2006); [2] Wide confidence intervals/low number of events limit the precision of this outcome; [3] HR indicates mortality risk. 2-year overall survival rate was 37% (95% CI 28%-45%) for HD-MVAC and 26% (95% CI 18%-34%) for MVAC; [4] HR indicates progression risk. 2-year progression-free survival rate was 24.7% (95% CI 17.1% to 32.3%) for HD-MVAC versus 11.6% (95% CI 5.9% to 17.4%) for MVAC.

Table 126. GRADE evidence profile: Docetaxcel & Cisplatin (DC) with GCSF versus MVAC with GCSF

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	DC	MVAC	Relative (95% CI)	Absolute	
Overall survival (mortality rate, median follow-up 25.3 months, range 3.2 to 51 months for surviving patients)											
1[1]	randomised trials	none	none	none	serious[2]	none	84/111 (75.7%)	74/109 (67.9%)	HR 1.52 (1.11 to 2.08)	Median OS, 9.3 vs. 14.2 mo	⊕⊕⊕O MODERATE
Progression-free survival (relapse rate during follow-up, median follow-up 25.3 months, range 3.2 to 51 months for surviving patients)											
1[1]	randomised trials	none	none	none	serious[2]	none	76/111 (68.5%)	65/109 (59.6%)	HR 1.73 (1.24 to 2.42)	Median TTP, 6.1 vs. 9.4 mo	⊕⊕⊕O MODERATE
Toxicity - Grade 3-4 Neutropenia (NCI Common Toxicity Criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	20/104 (19.2%)	37/103 (35.9%)	RR 0.54 (0.33 to 0.86)	165 fewer per 1000 (from 50 fewer to 241 fewer)	⊕⊕⊕O MODERATE
Toxicity - Grade 3-4 Thrombocytopenia (NCI Common toxicity criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	1/104 (1%)	6/103 (5.8%)	RR 0.17 (0.02 to 1.35)	48 fewer per 1000 (from 57 fewer to 20 more)	⊕⊕⊕O MODERATE
Toxicity - Grade 3-4 Anaemia (NCI Common toxicity criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	6/104 (5.8%)	8/103 (7.8%)	RR 0.74 (0.27 to 2.07)	20 fewer per 1000 (from 57 fewer to 83 more)	⊕⊕⊕O MODERATE
Toxicity - Grade 3-4 Neutropenic sepsis (NCI Common toxicity criteria)											
1	randomised trials	none	none	none	serious[2]	none	4/104 (3.8%)	12/103 (11.7%)	RR 0.33 (0.11 to 0.99)	78 fewer per 1000 (from 1 fewer to 104 fewer)	⊕⊕⊕O MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	none	serious[2]	none	1/111 (0.9%)	2/109 (1.8%)	RR 0.49 (0.05 to 5.34)	9 fewer per 1000 (from 17 fewer to 80 more)	⊕⊕⊕O MODERATE
Health-related quality of life											
0	no evidence available										

[1] Bamias 2004; [2] Wide confidence intervals / low number of events limit the precision of this outcome

Table 127. GRADE evidence profile: MVAC versus Gemcitabine & Cisplatin (GC)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute	
Overall survival (mortality rate, maximum follow-up 5 years)											
1[1]	randomised trials	none	none	none	none	none	176/203 (86.7%)	171/202 (84.7%)	HR 1.09 (0.88 to 1.34)	Median OS, 14 vs. 15.2 mo	⊕⊕⊕⊕ HIGH
Progression-free survival (progression or death rate, maximum follow-up 5 years)											
1[1]	randomised trials	none	none	none	none	none	184/203 (90.6%)	178/202 (88.1%)	HR 1.09 (0.89 to 1.34)	Median PFS, 7.7 vs. 8.3 mo	⊕⊕⊕⊕ HIGH
Toxicity - Grade 3-4 anaemia (WHO criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	55/203 (27.1%)	36/202 (17.8%)	RR 1.52 (1.05 to 2.21)	93 more per 1000 (from 9 more to 216 more)	⊕⊕⊕O MODERATE
Toxicity - Grade 3-4 thrombocytopenia (WHO criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	116/203 (57.1%)	42/202 (20.8%)	RR 2.75 (2.02 to 3.69)	364 more per 1000 (from 212 more to 559 more)	⊕⊕⊕O MODERATE
Toxicity - Grade 3-4 neutropenia (WHO criteria)											
1[1]	randomised trials	none	none	none	none	none	144/203 (70.9%)	166/202 (82.2%)	RR 0.86 (0.77 to 0.96)	115 fewer per 1000 (from 33 fewer to 189 fewer)	⊕⊕⊕⊕ HIGH
Neutropenic sepsis											
1[1]	randomised trials	none	none	none	serious[2]	none	2/203 (1%)	24/202 (11.9%)	RR 0.08 (0.02 to 0.35)	109 fewer per 1000 (from 77 fewer to 116 fewer)	⊕⊕⊕O MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	none	serious[2]	none	2/203 (1%)	5/202 (2.5%)	RR 0.40 (0.08 to 2.03)	15 fewer per 1000 (from 23 fewer to 25 more)	⊕⊕⊕O MODERATE
Health-related quality of life (measured with: EORTC quality of life questionnaire C30; Better indicated by higher values)											
1[1]	randomised trials	none	none	none	serious[2]	none	165	161	-	MD 0 higher (0 to 0 higher)[3]	⊕⊕⊕O MODERATE
Patient preferences for GC vs MVAC											
1[4]	observational studies	serious[5]	none	none	serious[2]	none			Not estimable[6]	-	⊕OOO VERY LOW

[1] von der Maase (2000/2005); [2] Low number of events limits precision; [3] Mean scores not reported. The authors state that quality of life was maintained on both arms throughout the study with both arms noting improvements in emotional functioning and pain. More GC-treated patients reported at least a 10 point improvement in fatigue compared to MVAC-treated patients (33% versus 28%). This difference was not statistically significant; [4] Aristides (2005); [5] Number and characteristics of respondents not reported. Oncology professionals interviewed as patient representatives; [6] Respondents were almost eight times more likely to choose GC over MVAC for a reduced incidence of neutropenic sepsis (OR 7.7, 95% CI 3.0-17.8, p<0.001). Respondents were four times more likely to choose GC over MVAC for reduced incidence of mucositis (OR 4.1, 95% CI 1.9-9.0), or serious weight loss (OR 3.9, 95% CI 2.1-7.3) Overall, respondents were willing to accept GC over MVAC with a probability of 0.9972, given an equal life expectancy of 60 weeks. This significant probability remained despite a hypothetical reduction in life expectancy to 45 weeks for patients treated with GC

Table 128. GRADE evidence profile: Dose dense MVAC (DD-MVAC) versus Dose dense Gemcitabine & Cisplatin (DD-GC)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DD-MVAC	DD-GC	Relative (95% CI)	Absolute	
Overall survival (follow-up median 52 months; assessed with: Mortality rate)											
1[1]	randomised trials	none	none	none	very serious[2]	none	45/63 (71.4%)	44/63 (69.8%)	Not reported *p=0.98*	-	⊕⊕OO LOW
Progression-free survival (follow-up mean 52.1 months)											
1[1]	randomised trials	none	none	none	very serious[2]	none	52/63 (82.5%)	47/63 (74.6%)	Not reported *p=0.36*	-	⊕⊕OO LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	none	very serious[2,3]	none	12/61 (19.7%)	8/59 (13.6%)	RR 1.45 (0.64 to 3.29)	61 more per 1000 (from 49 fewer to 311 more)	⊕⊕OO LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	none	very serious[2,3]	none	5/61 (8.2%)	5/59 (8.5%)	RR 0.97 (0.30 to 3.17)	3 fewer per 1000 (from 59 fewer to 184 more)	⊕⊕OO LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	none	very serious[2,3]	none	7/61 (11.5%)	6/59 (10.2%)	RR 1.13 (0.40 to 3.16)	13 more per 1000 (from 61 fewer to 220 more)	⊕⊕OO LOW
Grade 3-5 toxicities (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	none	very serious[2,3]	none	30/61 (49.2%)	26/59 (44.1%)	RR 1.12 (0.76 to 1.64)	53 more per 1000 (from 106 fewer to 282 more)	⊕⊕OO LOW
Treatment-related mortality											
1[1]	randomised trials	none	none	none	very serious[2,3]	none	2/63 (3.2%)	0/63 (0%)	RR 5.00 (0.24 to 102.10)	-	⊕⊕OO LOW
Health-related quality of life											
0	No evidence available										

[1] Bamias (2013); [2] Low number of events. Underpowered study. Trial closed early due to poor accrual; [3] Wide confidence interval (includes null value) limits precision

Table 129. GRADE evidence profile: Gemcitabine & Cisplatin & Paclitaxel (PCG) versus Gemcitabine & Cisplatin (GC)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCG	GC	Relative (95% CI)	Absolute	
Overall survival (mortality rate, follow-up median 4.6 years, maximum 6.8 years)											
1[1]	randomised trials	none	none	none	none	none	248/312 (79.5%)	256/314 (81.5%)	HR 0.85 (0.71 to 1.02)[2]	Median OS, 15.8 vs. 12.7 mo	⊕⊕⊕⊕ HIGH
Overall survival - Bladder tumour (mortality rate, follow-up median 4.6 years)											
1[1]	randomised trials	none	none	none	none	none	198/254 (78%)	213/259 (82.2%)	HR 0.80 (0.66 to 0.97)[3]	Median OS, 15.9 vs. 11.9 mo	⊕⊕⊕⊕ HIGH
Progression-free survival (progression or death rate, follow-up median 4.6 years)											
1[1]	randomised trials	none	none	none	none	none	269/312 (86.2%)	278/314 (88.5%)	HR 0.87 (0.74 to 1.03)	Median PFS = 8.3 vs. 7.6 mo	⊕⊕⊕⊕ HIGH
Severe acute toxicity (NCI Common Toxicity Criteria)											
1[1]	randomised trials	none	none	none	serious[4]	none	61/302 (20.2%)	45/305 (14.8%)	RR 1.37 (0.96 to 1.94)	52 more per 1000 (from 6 fewer to 139 more)	⊕⊕⊕O MODERATE
Grade 3-4 Neutropenia											
1[1]	randomised trials	none	none	none	none	none	194/302 (64.2%)	154/305 (50.5%)	RR 1.27 (1.11 to 1.46)	136 more per 1000 (from 56 more to 232 more)	⊕⊕⊕⊕ HIGH
Grade 3-4 Thrombocytopenia											
2[5]	randomised trials	none	none	none	none	none	119/345 (34.5%)	168/348 (48.3%)	RR 0.71 (0.6 to 0.86)	140 fewer per 1000 (from 68 fewer to 193 fewer)	⊕⊕⊕⊕ HIGH
Grade 3-4 Anaemia											
1[6]	randomised trials	none	none	none	serious[4]	none	9/42 (21.4%)	10/43 (23.3%)	RR 0.92 (0.42 to 2.04)	19 fewer per 1000 (from 135 fewer to 242 more)	⊕⊕⊕O MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	none	serious[4]	none	6/302 (2%)	3/305 (1%)	RR 2.02 (0.51 to 8)	10 more per 1000 (from 5 fewer to 69 more)	⊕⊕⊕O MODERATE
Health-related quality of life											
0	no evidence available										

[1] Bellmunt (2012); [2] The overall survival rate at 1 year was 61.4% with PCG, and 52.8% with GC; [3] In the 81% of patients in whom bladder was the site of the primary tumour, median overall survival was 15.9 months with PCG and 11.9 months with GC (p=.025); [4] Wide confidence intervals limit the precision of this outcome; [5] Bellmunt (2012); Lorusso (2005); [6] Lorusso (2005)

Table 130. GRADE evidence profile: MVAC versus Carboplatin & Paclitaxcel (CaP)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MVAC	CaP	Relative (95% CI)	Absolute	
Overall survival (follow-up median 32.5 months)											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none			Not estimable[3]	-	⊕OOO VERY LOW
Progression-free survival											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none			Not estimable[4]	-	⊕OOO VERY LOW
Toxicity - Grade 3 or higher neutropenia (NCI Common Toxicity Criteria)											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none	29/43 (67.4%)	12/41 (29.3%)	RR 2.30 (1.37 to 3.87)	380 more per 1000 (from 108 more to 840 more)	⊕OOO VERY LOW
Toxicity - Grade 3 or higher anaemia (NCI Common Toxicity Criteria)											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none	16/43 (37.2%)	2/41 (4.9%)	RR 7.63 (1.87 to 31.13)	323 more per 1000 (from 42 more to 1000 more)	⊕OOO VERY LOW
Toxicity - Grade 3 or higher thrombocytopenia (NCI Common Toxicity Criteria)											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none	9/43 (20.9%)	4/41 (9.8%)	RR 2.15 (0.72 to 6.43)	112 more per 1000 (from 27 fewer to 530 more)	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none	1/43 (2.3%)	1/41 (2.4%)	RR 0.95 (0.06 to 14.75)	1 fewer per 1000 (from 23 fewer to 335 more)	⊕OOO VERY LOW
Health-related quality of life (follow-up 10 months; measured with: Functional Assessment of Cancer Therapy - Bladder; Better indicated by higher values)											
1[1]	randomised trials	very serious[2]	none	none	serious[6]	none	43	41	-	MD 0 higher (0 to 0 higher)[7]	⊕OOO VERY LOW

[1] Dreicer 2004; [2] Underpowered trial - closed early because of slow accrual; [3] Numbers of patients alive at follow-up not reported, Hazard ratios not reported. Median overall survival was 15.4 months with MVAC, and 13.8 months with CaP (p=0.65); [4] Number of patients with disease progression not reported. Hazard ratios not reported. Median progression-free survival was 8.7 months with MVAC, and 5.2 months with CaP (p=0.24); [5] Wide confidence intervals, small sample size and/or low number of events limit the precision of this outcome; [6] Low number of participants assessed for quality of life at study entry (n=38) and at 10 month follow-up (n=14) which reduces the precision of this outcome; [7] Mean FACT-BL scores not reported - authors state there was no significant differences over time by treatment arm (p=0.33).

Table 131. GRADE evidence profile: Gemcitabine & Cisplatin (GC) versus Gemcitabine & Carboplatin (GCarbo)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	GC	GCarbo	Relative (95% CI)	Absolute	
Overall survival (mortality rate, follow-up median 7 months)											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none	7/55 (12.7%)	7/55 (12.7%)	HR not reported	Median OS, 12.8 vs. 9.8 mo[3]	⊕OOO VERY LOW
Disease progression (follow-up median 7 months)											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none	NR	NR	HR not reported	Median TTP, 8.3 vs. 7.7 mo[4]	⊕OOO VERY LOW
Toxicity - Grade3-4 Neutropenia (WHO criteria)											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none	19/55 (34.5%)	25/55 (45.5%)	RR 0.76 (0.48 to 1.21)	109 fewer per 1000 (from 236 fewer to 95 more)	⊕OOO VERY LOW
Toxicity - Grade 3-4 Thrombocytopenia (WHO criteria)											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none	17/55 (30.9%)	22/55 (40%)	RR 0.77 (0.46 to 1.29)	92 fewer per 1000 (from 216 fewer to 116 more)	⊕OOO VERY LOW
Toxicity - Grade 3-4 Anaemia (WHO criteria)											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none	11/55 (20%)	14/55 (25.5%)	RR 0.79 (0.39 to 1.58)	53 fewer per 1000 (from 155 fewer to 148 more)	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	randomised trials	very serious[2]	none	none	serious[5]	none	-	-	Not estimable[6]	-	⊕OOO VERY LOW
Health-related quality of life											
0	no evidence available										

[1] Dogliotti 2007; [2] Underpowered trial, insufficient follow-up; [3] Median survival was 12.8 months with GC, and 9.8 months with GCarbo (reported by authors as not clinically significant, hazard ratios not provided); [4] Median time to progression was 8.3 months (range 7.5-9.1) with GC, and 7.7 (range 5.1-10.3) with GCarbo, (reported by authors as not significant, hazard ratios not provided); [5] Wide confidence intervals / low number of events limit the precision of this outcome; [6] 14 deaths reported in Dogliotti (2007), 13 were not considered drug related. 1 patient in the GC group died of acute renal failure possibly related to cisplatin. No toxicity data available for this patient because blood sample not collected.

Table 132. GRADE evidence profile: MVAC versus M-CAVI (Methotrexate, Carboplatin, Vinblastine)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MVAC	M-CAVI	Relative (95% CI)	Absolute	
Overall survival (disease-related mortality rate, follow-up median 18 months, range 6-60 months)											
1[1]	randomised trials	none	none	none	very serious[2]	none	19/24 (79.2%)	18/23 (78.3%)	HR 0.49 (0.26 to 0.93)	Median DSS, 16 vs. 9 months[3]	⊕⊕OO LOW
Progression-free survival											
0	no evidence available										
Toxicity - Grade 3-4 Stomatitis											
1[1]	randomised trials	none	none	none	very serious[2]	none	5/24 (20.8%)	1/23 (4.3%)	RR 4.79 (0.6 to 37.95)	165 more per 1000 (from 17 fewer to 1000 more)	⊕⊕OO LOW
Toxicity - Grade 3-4 Thrombocytopenia											
1[1]	randomised trials	none	none	none	very serious[2]	none	1/24 (4.2%)	1/23 (4.3%)	RR 0.96 (0.06 to 14.43)	2 fewer per 1000 (from 41 fewer to 584 more)	⊕⊕OO LOW
Toxicity - Grade 3-4 Anaemia											
1[1]	randomised trials	none	none	none	very serious[2]	none	1/24 (4.2%)	1/23 (4.3%)	RR 0.96 (0.06 to 14.43)	2 fewer per 1000 (from 41 fewer to 584 more)	⊕⊕OO LOW
Treatment-related mortality											
1[1]	randomised trials	none	none	none	very serious[2]	none	1/24 (4.2%)	0/23 (0%)	RR 2.88 (0.12 to 67.29)	-	⊕⊕OO LOW
Health-related quality of life											
0	no evidence available										

[1] Bellmunt (1997); [2] Low number of participants/events and wide confidence intervals limits the precision of this outcome. HR calculated from p-value and observed number of events.

[3] Median disease-related survival was 16 months (range 3 to 24+) for MVAC, and 9 months (range 2 to 17) for M-CAVI (p= 0.03).

Table 133. GRADE evidence profile: Cisplatin-based chemotherapy versus Carboplatin-based chemotherapy

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cisplatin-based	Carboplatin-based	Relative (95% CI)	Absolute	
Overall survival (Mortality at 12 months)											
2[1]	randomised trials	very serious[2]	none	none	serious[3]	none	NR	NR	RR 0.775 (0.56 to 1.07)	-	⊕OOO VERY LOW
Progression-free survival											
0	no evidence available[4]										
Overall tumour response (partial+complete response, WHO definition)											
4[5]	randomised trials	very serious[2]	none	none	serious[3]	none	73/128 (57%)	54/128 (42.2%)	RR 1.34 (1.04 to 1.71)	143 more per 1000 (from 17 more to 300 more)	⊕OOO VERY LOW
Complete tumour response (WHO definition)											
4[5]	randomised trials	very serious[2]	none	none	serious[3]	none	23/128 (18%)	5/128 (3.9%)	RR 3.54 (1.48 to 8.49)	99 more per 1000 (from 19 more to 293 more)	⊕OOO VERY LOW
Toxicity											
4[5]	randomised trials	very serious[2]	none	none	none	none	-	-	Not estimable[6]	-	⊕⊕OO LOW
Health-related quality of life (follow-up 10 months; measured with: Functional Assessment of Cancer Therapy - Bladder; Better indicated by higher values)											
1[7]	randomised trials	very serious[2]	none	none	serious[8]	none	N=43	N=41	-	MD 0 higher (0 to 0 higher)[9]	⊕OOO VERY LOW

[1] Dreicer (2004); Dogliotti (2007); [2] Three of the included trials were closed early and were underpowered to detect clinically significant differences between arms; [3] Wide confidence intervals / low number of events limit the precision of this outcome; [4] Progression-free survival data could not be pooled; [5] 4 trials included in meta-analysis by Glasky (2012) - Bellmunt (1997); Dogliotti (2007); Dreicer (2004); Petrioli (1996); [6] Toxicity data could not be pooled. Trials generally report more severe toxicity with Cisplatin-based regimens compared with Carboplatin-based regimens; [7] Dreicer (2004); [8] Low number of participants assessed for quality of life at study entry (n=38) and at 10 month follow-up (n=14) which reduces the precision of this outcome [9] Mean FACT-BL scores not reported - authors state there was no significant differences over time by treatment arm (p=0.33).

Table 134. GRADE evidence profile: Gemcitabine & Carboplatin (GCarbo) versus Methotrexate, Carboplatin & Vinblastine (M-CAVI) in patients unfit for cisplatin

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	GCarbo	M-CAVI	Relative (95% CI)	Absolute	
Overall survival (mortality rate, follow-up median 4.5 years, maximum 7.8 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	110/119 (92.4%)	108/119 (90.8%)	HR 0.94 (0.72 to 1.02)	Median OS, 9.3 vs. 8.1 mo	⊕⊕⊕O MODERATE
Progression-free survival (progression or death rate, follow-up median 4.5 years, maximum 7.8 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	115/119 (96.6%)	113/119 (95%)	HR 1.04 (0.8 to 1.35)	Median PFS, 5.8 vs. 4.2 mo	⊕⊕⊕O MODERATE
Severe Acute Toxicity (SAT) (follow-up median 4.5 years; NCI-Common Toxicity Criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	11/118 (9.3%)	25/118 (21.2%)	RR 0.44 (0.23 to 0.85)	119 fewer per 1000 (from 32 fewer to 163 fewer)	⊕⊕⊕O MODERATE
Treatment-related mortality (follow-up median 4.5 years)											
1[1]	randomised trials	none	none	none	Serious[3]	none	3/119 (2.5%)	4/119 (3.4%)	RR 0.75 (0.17 to 3.28)	8 fewer per 1000 (from 28 fewer to 77 more)	⊕⊕⊕O MODERATE
Health-related quality of life (measured with: EORTC Quality of life questionnaire C30, measured until end of treatment; Better indicated by higher values)											
1[1]	randomised trials	none	none	none	Serious[4]	none	0	0	-	MD 0 higher (0 to 0 higher)[5]	⊕⊕⊕O MODERATE

[1] De Santis (2012); [2] Low number of events limit precision; [3] Wide confidence intervals and low number of events suggest imprecise results; [4] Low compliance (90% at baseline and less than 50% afterward) limits the precision of this outcome. Mean scores for each arm across time not reported; [5] Authors state there were no differences between the two treatment arms for changes in primary scale global health status/QoL from baseline to end of cycle 2.

Table 135. Outcome data from randomised trials of first-line chemotherapy for advanced/metastatic bladder cancer

HR, hazard ratio; OR, overall response; CR, complete response; Neu, neutropenia; Throm, thrombocytopenia; Anae, anaemia; Sep, neutropenic sepsis; Muc, mucositis; Leuc, leucopenia; Neuro, neurotoxicity; SAT, severe acute toxicity; Stoma, stomatitis; Gran, granulocytopenic fever

	Overall survival			**Progression-free survival**			**Grade 3-4 toxicities, %**				**Other, %**			**Quality of life**
Study/ comparators	**Rate, %**	**Median months**	**HR (95% CI)**	**Rate, %**	**Median months**	**HR (95% CI)**	**Neu**	**Throm**	**Anae**	**SAT**	**Sep**	**Muc**	**Toxic deaths (n)**	
von der Maase (2005)	5 yrs			5 yrs										QoL maintained over time on both arms, improved emotional functioning and pain.
GC (n=203)	13.4	14.0	1.09 (0.88-1.34)	9.4	7.7	1.09 (0.89-1.34)	71	57	27		1	1	1%	
vs. MVAC (n=202)	15.3	15.2	p=0.66	11.9	8.3	p=0.63	82	82	17		12	22	3%	
Bellmunt (2012)	4.6 yrs			4.6 yrs										
PCG (n=312)	20	15.8	0.85 (0.72-1.02)	14	8.3	0.87 (0.74-1.03)	64	35		20			6	
vs. GC (n=314)	18	12.7	p=0.75	11	7.6	p=0.113	51	52		15			3	
Bellmunt (2012)	Primary bladder tumours only													
PCG (n=254)		15.9	0.80 (0.66-0.97)											
vs. GC (n=259)		11.9	p=0.025											
Lorusso (2005)							Leuc				Neuro			
GC (n=43)		12.3		33	6.5		35	21	24		5	5		
vs. PCG (n=42)		15.3		29	8		49	36	20		0	0		
Bamias 2004														
MVAC +GCSF (n=109)	32	14.2	1.52 (1.11-2.08)		9.4	1.73 (1.24-2.42)	36	6	8		12		2	
vs. DC +GCSF (n=111)	24	9.3	p=0.0255		6.1	p=0.0029	19	1	6		4		1	
Sternberg 2006	7.3 yrs			7.3 yrs										
							Fever		WBC					
HD-MVAC (n=134)	24.6	15.1	0.76 (0.58-0.99)	18.7	9.5	0.73 (0.56-0.95)	10	22	20			10	1	
vs. MVAC (n=129)	13.2	14.9	(mortality HR)	10.1	8.1	p=0.017	26	17	62			17	1	

Study/ comparators	Overall survival			Progression-free survival			Grade 3-4 toxicities, %				Other, %			Quality of life
	Rate, %	Median months	HR (95% CI)	Rate, %	Median months	HR (95% CI)	Neu	Throm	Anae	SAT	Sep	Muc	Toxic deaths (n)	
Bamias 2013	1 yr			1 yr										
DD-MVAC (n=63) vs. DD-GC (n=63)	66 62	19 18		38 37	8.5 7.8		20 14	8 8	11 10	50 44			2 0	
Loehrer 1992	6 yrs	19.7 mo		6 yrs	19.7 mo									
							Leuc	Gran						
C (n=120) vs. MVAC (n=126)	1.6 6.8	8.2 12.5	p=0.002	1.6 3.7	4.3 10		1 24	0 10	1 1		1 6	0 17	0 5	
Mead 1998	1 yr													
							Fever							
CMV (n=108) vs. MV (n=106)	29 16	7 4.5	0.68 (0.51-0.90) p=0.0065 (Mortality HR)		5.5 3	0.55 (0.41-0.73) p=0.0001 (Risk of progression)	10 2	5 0					5 0	
Hillcoat 1989				2 yrs										
							Heam	Nausea						
CM (n=53) vs. C (n=55)		8.7 7.2	p=0.7	10 10	5.0 2.8	p=0.13	27 7	44 25				20 0	2 0	
Pizzocaro 1991														
							Leuc							
MVAC (n=14) vs. MC (n=14)							14 7	14 7	7 7			7 7		
Petrioli 1996	21 mo						G 2-4 Leuc							
MVEC (n=29) vs. MVECa (n=28)	25 7.4	13 9.5	p=0.3				37 58	21 26	25 10			17 16		
Dogliotti (2007)														
GC (n=55) vs. GCarbo (n=55)	64 37	12.8 9.8			8.3 7.7		35 46	31 38	20 26			4 11		
Dreicer 2004														FACT-BL: no significant differences over time between study arms
MVAC (n=44) vs. CaP (n=41)		15.4 13.8	p=0.65		8.7 5.2	p=0.24	67 29	21 10	37 5			9 0	1 1	

Study/ comparators	Overall survival			Progression-free survival			Grade 3-4 toxicities, %				Other, %			Quality of life
	Rate, %	Median months	HR (95% CI)	Rate, %	Median months	HR (95% CI)	Neu	Throm	Anae	SAT	Sep	Muc	Toxic deaths (n)	
Bellmunt 1997														
							Stoma							
MVAC (n=24)	12.5	16					21	3	3		0		1	
vs. M-CAVI (n=23)	21.7	9	p=0.03				4	3	3		3		0	
De Santis (2012)	4.5 yrs			4.5 yrs										No differences between arms for changes in global QoL. Inconclusive data.
									Leuc					
GCarbo (n=119)	7.6	9.3	0.94 (0.72-1.22)	3.4	5.8	1.04 (0.80 to 1.35)	53	48	45	9			3	
vs. M-CAVI (n=119)	9.2	8.1	p=0.64	5.0	4.2		64	19	47	21			4	

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Reason: not relevant to PICO

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Reason: not relevant to PICO (adjuvant chemotherapy)

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Reason: not RCT

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Reason: feasibility study, majority breast cancer patients

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Reason: Intervention not relevant to PICO (CISCA)

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Reason: Intervention not relevant to PICO (oxaliplatin)

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Reason: study record, no data

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Reason: comment on Bamias (2005)

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Reason: not randomised trial

Evidence tables

BCa, bladder cancer; TCC, transitional cell cancer; GCarbo, Gemcitabine/Carboplatin; M-CAVI, Methotrexate/Carboplatin/Vinblastine; PS, performance status; GFR, Glomerular filtration rate; GC, Gemcitabine/Cisplatin; GCP, Gemcitabine/Cisplatin/Paclitaxel; MVAC, Methotrexate/Vinblastine/Adriamycin/Cisplatin; CaP, Carboplatin/Paclitaxel; HD-MVAC, High-dose Methotrexate/Vinblastine/Adriamycin/Cisplatin; NCI-CTC, National Cancer Institute Common Toxicity Criteria; GCSF, granulocyte colony-stimulating factor; CISCA, Cisplatin/Doxorubicin/Cyclophosphamide; SAT, severe acute toxicity

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
De Santis (2009) Phase II EORTC 30986	N=178, chemo-naive, TCC of the urinary tract, unresected lymph nodes (N+), distant metastases (M1, stage IV), or unresectable primary BCa (T3-T4). All unfit for cisplatin – WHO PS 2 and/or GFR>30-60 mL/min.	Median age 71 (GCarbo) and 72 (MVC), range (34-86) 78% M / 22% F	Median GFR 50 (30-125) for GCarbo and 47 (30-115 mL/min) for M-CAVI	GCarbo = Gemcitabine (1g/m^2 over 30mins days 1 & 8) plus Carboplatin (4.5 x (GFR)+25)mg over 1 hour day 1, every 3 weeks. Median cycles=4.5 (1-10). Dose reductions were required in 72% and delays were required in 76% in the GC arm.	M-CAVI = Methotrexate (30mg/m^2 iv days 1, 15 and 22) plus Vinblastine (3mg/m^2 iv days 1, 15 & 22) plus Carboplatin (4.5 x (GFR)+25)mg over 1 hour day 1, every 28 days. Median cycles=3 (1-23). Dose reductions were required in 84% and delays were required in 61% in the M-CAVI arm.	Tumour response Toxicity – NCI-CTC. SAT defined by death, grade 4 thrombocytopenia with bleeding, grade 3 to 4 renal toxicity, neutropenic fever, or mucositis	Not stated	Concealment of treatment allocation, blinding of outcomes assessment, and intent-to-treat analysis not reported.
De Santis (2012) Phase III EORTC 30986	N=238, chemo-naive, TCC of the urinary tract, unresected lymph nodes (N+), distant metastases (M1, stage IV), or unresectable primary BCa (T3-T4). All unfit for cisplatin – WHO PS 2 and/or GFR>30-60 mL/min.	Median age 71 (34-87) 78% M / 22% F	Median GFR 49 (30-128) mL/min. 16% WHO PS 0 39% WHO PS 1 45% WHO PS 2 Primary tumour: 74% BCa, 12% renal pelvis, 10% ureter, 2% urethra. 79% liver metastases, 51% visceral metastases	GCarbo = Gemcitabine (1g/m^2 over 30mins days 1 & 8) plus Carboplatin (4.5 x (GFR)+25)mg over 1 hour day 1, every 3 weeks. The majority of patients received four cycles of chemotherapy. 25 (21%) stopped the treatment due to toxicity. Dose reductions were required in 73% and delays were required in 71% in the GC arm.	M-CAVI = Methotrexate (30mg/m^2 iv days 1, 15 and 22) plus Vinblastine (3mg/m^2 iv days 1, 15 & 22) plus Carboplatin (4.5 x (GFR)+25)mg over 1 hour day 1. Treatment cycles every 28 days. 26 (22%) stopped the treatment due to toxicity. Dose reductions were required in 85% and delays were required in 60% in the M-CAVI arm	Overall survival Toxicity (as above) Quality of life (EORTC QLQ-C30) Progression-free survival	Median 4.5 years, maximum 7.8 years	Concealment of treatment allocation and blinding of outcomes assessment not reported. Intent-to-treat analysis was used for survival outcomes.
Dogliotti (2007) Multicentre Phase II	N=114 (110 analysed) Previously untreated, locally advanced (T3b-T4b) or metastatic (N2, N3, M1) TCC of the urothelium. PS 0-2,	Median age 67 (32-80) 86% M / 14% F	47% Zubrod PS 0 43% Zubrod PS 1 10% Zubrod PS 2 9% Grade 3 (T3b-T4a) 91% Grade 4 (T4b)	GC(n=55): Gemcitabine 1.25g/m^2 (30 min infusion) days 1 & 8, plus Cisplatin 70mg/m^2 day 2, every 3 weeks. Patients received a median of 4 cycles (range	GCarbo (n=55): Gemcitabine (as previous) plus Carboplatin AUC 5 day 2 every 3 weeks. Patients received a median of 4 cycles (range 1-6). Maximum of either schedule was 6 cycles.	Toxicity (WHO criteria) Tumour response (WHO criteria) Progression Overall survival	Median 7.2 months for GC and 6.9 months for GCarbo	No method of randomisation. Concealment of treatment allocation, blinding of

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
	life expectancy of >12weeks, adequate renal function			1-6).				outcomes assessment, and ITT analysis not reported. Underpowered to detect differences in response and OS.
Lorusso (2005) Phase II	N=85, chemo-naive, proven metastatic or unresectable TCC of urinary tract. ECOG PS 0 to 2, adequate bone marrow, liver function and renal function. No pure adeno or squamous carcinoma	Median age 69 95% M / 5% F	Metastatic sites were: locally advanced only 24, nodal/soft tissue only 19, liver 14, bone 12, lung 15, peritoneum 1	GC = Gemcitabine 1g/m^2 days 1, 8 & 15, plus Cisplatin 70mg/m^2 day 2 every 4 weeks	PCG = Paclitaxel 70mg/m^2, Gemcitabine 1g/m^2, Cisplatin 70mg/m^2, days 1 and 8, every 3 weeks. Maximum of 6 cycles	Tumour response-(WHO criteria) Progression Overall survival Toxicity (WHO)		Open-label trial. Method of randomisation not stated. Follow-up time not stated.
von der Maase (2000) Mulitcenter Phase III	N=405, chemo naive, 34% locally advanced (T3-4, N2, N3) or 66% metastatic (M1) TCC of urotheliam. Karnofsky PS >70 and adequate marrow and renal function	Median age 63 79% M / 21% F	80% Karnofsky PS ≥ 80 13% prior intravesical therapy 39% prior cystectomy 12% prior radiation 47% visceral metastases	GC (n=203) = Gemcitabine 1g/m^2 (30-60 min infusion) days 1, 8 & 15 plus Cisplatin 70mg/m^2 day 2 Median 6 cycles 63% with no dose adjustments – most G omissions on day 15	MVAC (n=202) = Methotrexate 30mg/m^2 days 1, 5 and 22, plus Vinblastine 3mg/m^2 days 2, 15 and 22, plus Adriamycin 30mg/m^2 day 2, plus Cisplatin 70mg/m^2 day 2. Cycles were every 28 days for 6 weeks. Median 4 cycles. 37% with no dose adjustments– most adjustments on day 15 for M& V	Tumour response (WHO) criteria Time to progression Overall survival Toxicity (WHO criteria) Quality of life (EORTC QLQ-C30)	Median 19 months	Concealment of allocation not reported. Outcome assessment not blinded (but response confirmed by an independent reviewer). von der Maase (2005) reported 5-year follow-up data
Loehrer (1992)	N=269 (246 analysed), chemo naive incurable advanced metastatic carcinoma of the urothelium. Karnofsky PS ≥60%, adequate	Median age 65 (30-82) 81% M/19% F	Median PS 80% (range 60-100) Previous RT 27% (C), 23% (MVAC) Previous RC 36% (C), 33% (MVAC)	C (n=126): Cisplatin i.v. (70 mg/m^2) alone day 1. Cycles were repeated every 28 days until tumour progression or a maximum of six cycles	MVAC (n=120): Cisplatin i.v. (70 mg/m^2) day 2, plus Methotrexate 30 mg/m^2 on days 1, 15, 22, Vinblastine 3 mg/m^2 on days 2, 15, 22 plus Doxorubicin 30 mg/m^2 on day	Overall survival Progression-free survival Tumour response Toxicity	Median 19.7 months	6 year follow-up of overall survival reported in Saxman (1997)

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
	renal and marrow function		Primary tumour site bladder 83% (C), 90% (MVAC) Lung,liver and/or bone metastases 56% (C), 51% (MVAC)		2, every 28 days until tumour progression or a maximum of six cycles			
Sternberg (2001) Phase III EORTC 30924	N=263, metastatic or locally advanced TCC of the urinary tract (bladder, ureter, renal pelvis). No prior systemic cytotoxic or biologic treatment, WHO PS 0 to 2. Adequate renal and liver function	Mean age 62 (32-81) 81% M / 19% F	Median WHO PS was 1. 36% and 28% had visceral metastases; 64% and 72% did not have lung, liver or bone metastases; 20% and 15% had prior RT; 73% and 75% had prior surgery, respectively, for MVAC and HD-MVAC Tumour site: 85% bladder, 10% renal pelvis	HD-MVAC (n=134): Methotrexate 30 mg/m^2 day 1, Vinblastine 3 mg/m^2 day 2, Adriamycin 30 mg/m^2 day 2 and Cisplatin 70 mg/m^2 day 2. Plus GCSF administered on days 4–10, every 14 days. Median 6 cycles (1 to 12). Treatment duration 12 weeks (4 to 40)	MVAC (n=129): Methotrexate 30 mg/m^2 days 1, 15 and 22; Vinblastine 3 mg/m^2 days 2, 15 and 22; Adriamycin 30 mg/m^2 day 2; and Cisplatin 70 mg/m^2 day 2, every 28 days. Median 4 cycles (1 to 8). Treatment duration 21 weeks (2 to 28)	Tumour response (WHO criteria) Overall survival Progression-free survival Toxicity (WHO criteria)	Median 38 months, maximum 74 months	Appears to be an open-label trial as blinding of treatment allocation and outcome assessment not reported. Method of randomisation not reported.
Sternberg (2006) Phase III long-term follow-up	See above	See above	See above	See above	See above	Overall survival Progression-free survival Time-to-progression Response rate Toxicity	Median 7.3 years	7.3 year follow-up of EORTC 30924 (Sternberg, 2001)
Dreicer (2004) Phase III	N=80, chemo naive, TCC with progression, regional or metastatic disease, PS 0-2, adequate renal and marrow function	Median age 64 76% M / 24% F	39% PS 0, 45% PS 1, 14% PS 2 31% Bone and/or liver metastases	CaP: Paclitaxel over 3 hours 225 mg/m2 i.v day 1 followed by a fixed dose of Carboplatin (targeted area under the concentration-time curve [AUC] of 6) i.v. over 30 minutes every 3 weeks for a maximum of 6 treatment cycles Median 6 cycles. 3 (9%) patients discontinued	MVAC: Methotrexate i.v. 30 mg/m2 days 1, 15, and 22, plus Vinblastine 3 mg/m2 i.v. on Days 2, 15, and 22; Adriamycin at a dose of 30 mg/m2 i.v. on day 2, plus Cisplatin 70 mg/m2 i.v. over 2 hours day 2 with adequate hydration. Repeated every 28 days, maximum of 6 cycles. Median 5.5 cycles. 6 (17%)	Tumour response Toxicity – NCI-CTC Overall survival Progression-free survival Quality of life (FACT-BL)	Median 32.5 months	Underpowered - failed to reach accrual goal. No method of randomisation stated. No blinding of treatment allocation or outcome assessment.

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
				therapy because of toxicity	patients discontinued therapy because of toxicity			
Bamias (2004) Phase III	N=220, chemo-naive inoperable, metastatic, or recurrent (after surgery and/or radiotherapy) carcinoma of the urothelial tract, <75 years old, adequate marrow and liver function. PS 0-2.	Median age 65 (32-75) 90% M / 10% F	48% PS 0, 32% PS 1, 18% PS 2* Primary tumour: 84% bladder, 10% renal pelvis, 7% ureter 86% TCC, 4% squamous carcinoma, 2% adenocarcinoma, 4% mixed. 51% visceral metastases 40% removal of primary site, 18% radiotherapy, 12% prior adjuvant or neo-adjuvant chemo.	MVAC (n=109): Methotrexate 30 mg/m^2 and Vinblastine 3 mg/m^2 on days 1, 15, and 22, and Cisplatin 70 mg/m^2 and doxorubicin 30 mg/m^2 on day 1, every 4 weeks. GCSF was administered on days 7, 8, 9, 25, and 26	DC (n=111): Docetaxel 75 mg/m^2 and Cisplatin 75 mg/m^2 every 3 weeks. In both arms, Cisplatin was administered as a 1-hour infusion with adequate pre- and posthydration. GCSF was administered on days 5 to 9. Maximum 6 cycles unless progression or unacceptable toxicity, or if the patient refused to continue. Treatment was allowed to continue beyond the sixth cycle if it was believed to benefit the patient.	Overall survival Time-to-progression Tumour response (WHO critera) Toxicity – NCI-CTC	Median for surviving patients 25.3 months (3.2 to 51)	Method of randomisation not stated. Appears to be an open-label trial as concealment of allocation and outcome assessment is not reported. More patients with PS 0 and fewer with PS 2 in the MVAC arm compared with the DC arm at baseline (P = .040).
Bellmunt (2012) Phase III EORTC 30987	N=626, chemo-naive stage IV locally advanced (T4b, any N; or any T, N2-3) or metastatic TCC of the urothelium (pure or mixed). WHO PS 0 or 1, life expectancy of >12weeks, adequate renal function	Median age 61 (27-80) 82% M / 18% F	40% nonvisceral metastases, 48% visceral metastases Primary tumour: 82% bladder, 8% renal pelvis, 5% ureter, 3% urethra Prognostic risk group: 31% low, 43% intermediate, 26% high	PCG (n=312): Sequential administration of Paclitaxel 80 mg/m^2 days 1 and 8, before the same doses of Gemcitabine and Cisplatin as in the GC arm on day 1. Paclitaxel and Gemcitabine were administered at the same doses on day 8, every 21 days. Maximum of 6 cycles, unless progression or unacceptable toxicity. 44 (15%) stopped treatment due to toxicity. Dose reductions were required in 77% and delays	GC (n=314): Gemcitabine 1,000 mg/m^2 was administered on days 1, 8, and 15, and Cisplatin 70 mg/m^2 was administered on day 2, every 28 days. 48 (16%) stopped treatment due to toxicity. Dose reductions were required in 76% and delays were required in 58%.	Overall survival Progression-free survival Tumour response (RECIST) Toxicity – NCI-CTC	median 4.6 years (maximum, 6.8 years)	Open-label trial. Response rate assessed by blinded review.

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
				were required in 59%.				
Bellmunt (2007) Phase II	N=47, chemo-naive, surgically incurable advanced carcinoma of the bladder with bidimensionally measurable mass, adequate renal and marrow function, Karnofsky PS ≥60	Median age 65 (36-75) 94% M / 6% F	Median PS = 80 (range 60-100) 83% TCC (pure) 17% mixed histology (more mixed histology in MVAC group) 36% lymph node metastases 64% visceral metastases	M-CAVI (n=23): Methotrexate 30mg/m^2 i.v. days 1, 15 & 22; Carbolplatin 300mg/m^2 AUC 5 day 2; Vinblastine 3mg/m^2 days 2, 15 & 22, every 28 days.	MVAC (n=24): Cisplatin 70mg/m^2 day 2; Methotrexate 30mg/m^2 days 1, 15 & 22; Vinblastine 3mg/m^2 days 2, 15 & 22; Doxorubicin 30mg/m^2 day 2, every 28 days. No GCSF used in either arm.	Tumour response Overall survival Toxicity (WHO criteria)	Median 18+ months, range 6-60	1 MVAC patient died from toxicity and was excluded from response analysis. Trial terminated before reaching planned accrual.
Mead (1998)	N=214, chemo naive, metastatic or T4b TCC of urothelial tract. Fit for cisplatin – normal blood count and GFR >50ml/min.	Median age 64 78% M / 22% F	WHO PS 0 26%, PS 1 48%, PS 2 19%, PS 3 7% 89% primary bladder cancer 25% previous surgery, 49% previous radiotherapy ±surgery 55% visceral metastases 35% nodal metastases 5% T4b at presentation	MV (n=106): Methotrexate 30mg/m^2 days 1 &8, Vinblastine 4mg/m^2 days 1&8, 21 day cycle, for 6 cycles or until disease progression	CMV (108): Methotrexate 30mg/m^2 days 1 &8, Vinblastine 4mg/m^2 days 1&8, Cisplatin 70mg/m^2 day 2, 21 day cycle, for 6 cycles or until disease progression	Overall survival Progression-free survival Toxicity Tumour response	Not reported (1 year survival stated)	
Hillcoat (1989)	N=108, chemo naive, age ≤75 years, PS 0-3, recurrent or metastatic TCC of the urothelial tract, fit for cisplatin therapy	Median age 53 (MC), 65 (C), range 40-75. 76% M / 24% F	32% ECOG PS 0, 36% PS 1, 13% PS 2, 10% PS 3. 38% no prior treatment 57% radiotherapy	C (n=55): Cisplatin 80mg/m^2 day 1 every 4 weeks	CM (n=53): Methotrexate 50mg/m^2 on days 1 & 15, plus Cisplatin 80mg/m^2 on day 2 every 4 weeks	Tumour response Toxicity Overall survival	Range 2 to 5 years	Underpowered to detect differences in response rates
Petrioli (1996) Phase II	N=57, chemo naive recurrent or metastatic bladder cancer, ECOG PS ≤3, age <75 years,	Median age 65 (47-75)	46% ECOG PS ≤1, 42% PS ≤2, 12% PS ≤3 60% cystectomy, 14%	MVEC (n=29): Cisplatin 70mg/m^2 day 2, Methotrexate 30mg/m^2 days 1,15 &22, Vinblastine	MVECa (n=28): Carboplatin 250mg/m^2 day 1, Methotrexate 30mg/m^2 days 1,15 &22, Vinblastine 3mg/m^2 days 2, 15	Tumour response Toxicity (WHO criteria) Overall survival	Median 21 months (12-31)	Included in meta-analysis of cisplatin-based versus

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Comparison/control arm	Outcomes	Length of follow-up	Additional comments
	ANC of 1500/mm^3 or more, normal platelet count, serum creatinine and bilirubin of 1.5mg/dL or less	77% M / 23% F	adjuvant chemotherapy	3mg/m^2 days 2, 15 &22, Epirubicin 50mg/m^2 day 2, every 4 weeks. GCSF given daily when ANC >1000/mm^3 Median 4.5 cycles, range 1-12	&22, Epirubicin 50mg/m^2 day 2, every 4 weeks. GCSF given daily when ANC >1000/mm^3 Median 5 cycles, range 2-12			carboplatin-based chemotherapy
Pizzocaro (1991)	N= 28, chemo naive, metastatic TCC of the urinary tract, <70years old, ECOG PS 0-2	Median age 58 (43-68) 75% M / 25% F	81% bladder cancer, 11% renal pelvis cancer	MVAC (n=14): Methotrexate 30mg/m^2 day 1 &15, Vinblastine sulphate 3mg/m^2 day 2 &15, Adriamycin 30mg/m^2 day 2, Cisplatin 70mg/m^2 over 30-60mins, every 4 weeks	MP (n=14): Methotrexate 300mg/m^2 diluted in 250ml normal saline day 1, hydration continued on days 2 and 3, on which days folinic acid rescue 9mg/m^2 every 6 hours, Cisplatin 100mg/m^2 day 4, every 3 weeks	Tumour response Toxicity (WHO criteria)	Not reported	Method of randomisation not stated.
Bamias (2013)	N=130, inoperable, metastatic or recurrent TCC of urothelial tract. Adequate bone marrow and liver function creatinine>50ml/min, PS 0 or 1. Prior neo/adjuvant Ct allowed if given over 12mo before study	DD-MVAC: Median age 66 (35-76) 84% male, 16% female DD-GC: Median age 65 (34-80) 87% male, 13% female	DD-MVAC: 89% bladder, 6% pelvis. 32% primary surgery, 43% visceral mets, 67% ECOG 0. DD-GC: 78% bladder, 14% pelvis. 37% primary surgery, 30% visceral mets, 49% ECOG 0.	DD-MVAC: Methotrexate 30mg/m^2, Vinblastine 3mg/m^2, Cisplatin 70mg/m^2, Doxorubicin 30mg/m^2. Every 2 wks with GCSF support (days 5-9). Minimum 6 cycles (max 12) unless progression, intolerable toxicity or patient withdrawal of consent.	DD-GC: Gemcitabine 2500mg/m^2, Cisplatin 70mg/m^2. Every 2 wks with GCSF support (days 5-9). Minimum 6 cycles (max 12) unless progression, intolerable toxicity or patient withdrawal of consent.	Overall survival Progression-free survival Tumour response (RECIST) Toxicity – NCI-CTC	Median 52.1 mo	Adequate randomisation. Open-label study. Study discontinued due to low accrual. Underpowered study.

Health Economic Evidence: What are the comparative patient outcomes for treating metastatic bladder cancer with first-line chemotherapy

Review questions

What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

Table 136: Pico Table For The Optimal First-Line Chemotherapy Regimens For Treating Metastatic Bladder Cancer

Population	Intervention	Comparison	Outcomes
Patients with incurable locally advanced or metastatic bladder cancer Cisplatin fit (GFR >60 PS 0/1)	Chemotherapy agents for first-line chemotherapy (alone or in combination): • Methotrexate, Vinblastine, Adriamycin, Cisplatin, Gemcitabine, Carboplatin • Paclitaxel • Docetaxel	Each other (Cisplatin vrs Non Cisplatin) No treatment	• Overall survival • Progression free survival • Treatment-related mortality • Treatment related morbidity • Health-related quality of life, inc patient reported outcomes

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO
- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

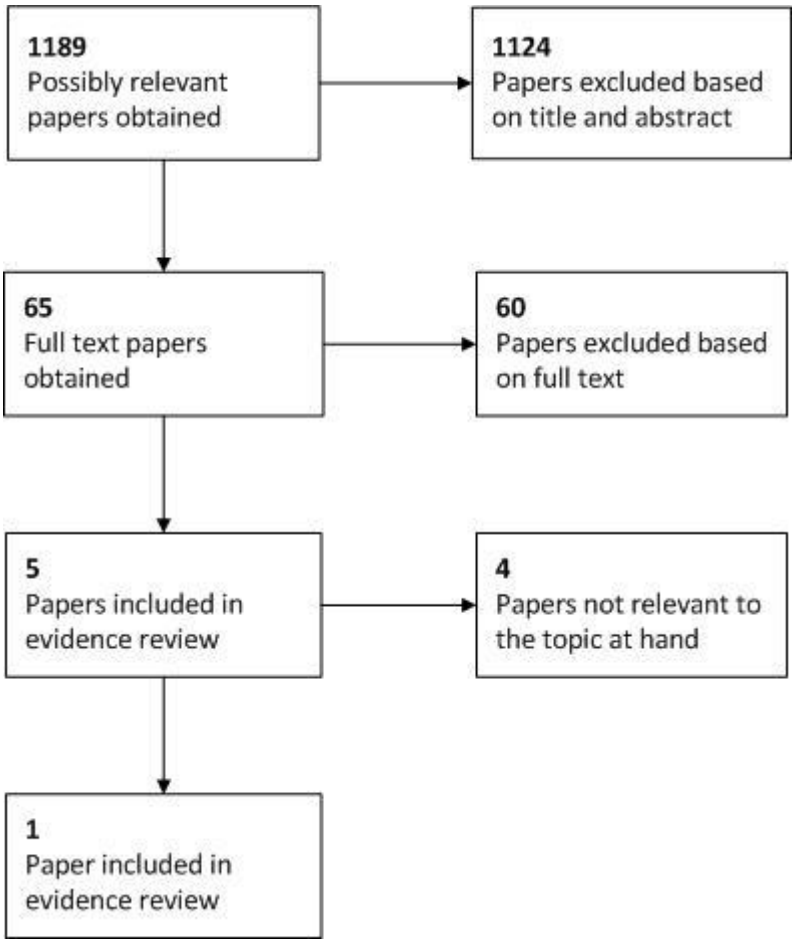
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

Three searches for economic evidence were run over the development of the guideline; one at the start of the process, an update midway through and a further update at the end of the process. The diagram below shows the combined results of the three searches and illustrates the sifting process.

Figure 73: Summary Of Evidence Search And Sifting Process For This Topic



It can be seen that, in total, 1,189 possibly relevant papers were identified. Of these, 1,124 papers were excluded at the initial sifting stage based on the title and abstract while 65 full papers were obtained for appraisal. A further 56 papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, nine papers were included in the systematic review of the economic evidence for this guideline.

One of these nine papers related to the topic at hand and was thus included in the review of published economic evidence for this topic; Robinson et al. 2004. The study included a cost-

effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

Quality and applicability of the included study

Robinson et al. 2004 was deemed to be only partially applicable to the decision problem that we are evaluating because the utility values were not directly reported by patients (as recommended by NICE). Instead they were elicited from healthcare professionals.

Potentially serious limitations were identified with the analysis. In particular, a potential conflict of interest was identified as the study was funded by the manufacturer of one of the therapies under consideration (Eli Lilly and Co, manufacturers of Gemcitabine). In addition, further sensitivity analysis could have been conducted to better explore uncertainty.

Table 137: Table Showing Methodological Quality And Applicability Of The Included Study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		
Potentially serious limitations		Robinson et al. 2004
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Robinson et al. 2004 are summarised in the modified GRADE table below.

Table 138: Modified Grade Table Showing The Included Evidence On The Optimal First-Line Chemotherapy Regimens For Treating Metastatic Bladder Cancer

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Robinson et al. 2004	Patients with locally advanced or metastatic bladder cancer.	Methotrexate / vinblastine / doxorubicin / cisplatin (MVAC)	**Base case estimate:** £9,633	Not reported	Reference standard			One-way sensitivity analyses were conducted on unit cost and length of stay parameters by varying original values by ±25%. The authors concluded that the model was robust to these changes. The authors considered the uncertainty	Partly applicable. The evaluation considers the UK health system. However, the utility values were not directly reported by patients (as recommended by NICE). Instead they were elicited from healthcare professionals.	Potentially serious limitations. Potential conflict of interest as the study was funded by Eli Lilly and Co, the manufacturer of one of the therapies under consideration (Gemcitabine). In addition, further sensitivity analysis could have been conducted to better explore
		Gemcitabine / cisplatin (GC)	**Base case estimate:** £12,609	Not repored	**Base case estimate:** £2,976 **Unfavourable (Upper) CI estimate:** £3,526 **Favourable (lower) CI estimate:** £2,427	**Base case estimate:** 0.130 QALYs **Unfavourable (lower) CI estimate:** 0.105 QALYs **Favourable (upper) CI estimate:** 0.188 QALYs	**Base case estimate:** £22,925 per QALY **Unfavourable CI estimate:** £33,589 per QALY **Favourable CI estimate:** £12,911 per QALY			

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
								shown in the CI calculations to be the only major source of uncertainty within the model. Probabilistic sensitivity analysis (PSA) was not conducted.		uncertainty. .
	Comments: The analysis was an atypical health economic evaluation because a decision analytic model was not constructed. Instead, the authors combined the results of a costing analysis based on a clinical trial with a parallel cross-sectional utility study.									

Evidence statements

The base case results of the cost-effectiveness analysis showed that, in comparison to the MVAC regimen, the combination of gemcitabine and cisplatin provided one additional quality adjusted life year (QALY) at a cost of £22,925. This ICER value is slightly higher than the threshold typically adopted by NICE (£20,000 per QALY) and so gemcitabine and cisplatin would not strictly be considered cost-effective.

Exceptions are made in instances where there may be some aspects that are not captured in the model. In this case, the cost of gemcitabine used in the model is unlikely to reflect the cost in current practice as the drug has come off patent in the intervening years. With the lower cost of gemcitabine in current practice, it is possible that the cost-effectiveness result would be improved significantly and could fall below the threshold of £20,000 per QALY.

However, there were concerns about the utility values that were used in the model as they were derived from healthcare professionals rather than patients and thus the QALY estimates may be unreliable. Furthermore, the applicability of this study to current practice is debatable as the MVAC regimen used in the study has largely been replaced with a more efficacious accelerated MVAC regimen.

Thus, overall, the available evidence base was not considered to provide a reliable estimate of cost-effectiveness that is relevant to current clinical practice.

References

1. Robinson P, Maase Hv, Bhalla S, Kielhorn A, Artistides M, Brown A, Tilden D. Cost-utility analysis of the GC versus MVAC regimens for the treatment of locally advanced or metastatic prostate cancer. *Expert Rev Pharmacoecon Outcomes Res.* 2004;**4**(1):27-38.

Full evidence table

The full details of the study included in the evidence review are presented in the evidence table below.

Table 139: Full evidence table showing the included evidence on the optimal first-line chemotherapy regimens for treating metastatic bladder cancer

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Author: Robinson et al. **Year:** 2004 **Country:** England and Wales	**Type of analysis:** Cost-effectiveness analysis with quality adjusted life years (QALYs) used as the effectiveness measure (therefore a cost-utility analysis). **Model structure:** A decision-analytic model was not constructed. Instead, the authors combined the results of a costing analysis based on a clinical trial with a cross-sectional utility study. **Cycle length:** Not applicable **Time horizon:** Lifetime horizon based on the overall survival in the clinical trial upon which the analysis is based. This amounts to 13.8 months in patients treated with Gemcitabine / cisplatin (GC) and 14.8 months in patients treated with Methotrexate / vinblastine /	**Inclusion criteria:** Not reported but presumably conforms to the clinical trial upon which it is based. **Exclusion criteria:** Not reported but presumably conforms to the clinical trial upon which it is based. **Base case (population):** Patients with locally advanced or metastatic prostate cancer. **Sample size:** The number of participants in the clinical trial upon which the analysis is based were: • 203 patients in	Two chemotherapy regimens were evaluated: 1. Gemcitabine / cisplatin (GC) 2. Methotrexate / vinblastine / doxorubicin / cisplatin (MVAC)	**Base case** **Effectiveness:** Willingness to trade time (WTTT) Utility gain on treatment ***Utility gain over life expectancy*** **Costs** ***GC regimen*** Study medications Inpatient administrations Outpatient administrations Hospitalisations Medical procedures Blood transfusions Health professional visits Concomitant medications ***Total*** ***MVAC regimen*** Study medications Inpatient administrations Outpatient administrations Hospitalisations Medical procedures Blood transfusions Health professional visits Concomitant medications ***Total***	 25.4 weeks 0.423 ***0.130 QALYs*** £3,899 £2,716 £4,052 £1,205 £238 £6 £123 £3,70 ***£12,609*** £885 £2,356 £3,375 £1,732 £249 £3 £127 £907 ***£9,633***	**Funding:** The study was funded by Eli Lilly and Co. **Comments**

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	doxorubicin / cisplatin (MVAC). **Perspective:** Third party payer perspective – NHS in England and Wales. **Source of base-line data:** Base-line data was not required for the economic analysis. **Source of effectiveness data:** A phase III clinical trial comparing MVAC and GC in patients with advanced bladder cancer provided the clinical data input to the model (von der Maase et al. 2000). The key findings of the trial were that there were no significant differences in survival time and time to disease progression in patients treated with MVAC and GC. However, patients treated with GC experienced a superior toxicity profile in comparison to patients treated with MVAC.	the GC arm • 202 patients in the MVAC arm **Age:** Not reported but presumably conforms to the clinical trial upon which it is based. **Gender:** Not reported but presumably conforms to the clinical trial upon which it is based. **Subgroup analysis:** No subgroup analyses were conducted.		***Incremental cost*** **ICER (cost per QALY):** The authors also presented cost-effectiveness results using upper and lower confidence limits based on upper and lower CIs of utilities and costs. The results of a favourable scenario (lower incremental cost CI and upper incremental QALY CI) and an unfavourable scenario (upper incremental cost CI and lower incremental QALY CI) were presented. N.B. The authors appear to have made a mistake when presenting these results by applying the wrong incrmental cost CI in the favourable and unfavourable scenarios. Amended results are presented here. **Unfavourable confidence interval limit** **Effectiveness:** Willingness to trade time (WTTT) Utility gain on treatment ***Utility gain over life expectancy***	***£2,976*** ***£22,925*** 20.54 weeks 0.342 ***0.105 QALYs***	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	This effectiveness data was not modelled as such. Rather it was combined with a separate utility study to estimate QALYs. Thus, patients receiving each regimen would get the survival time indicated by the trial multiplied by the appropriate utility value (described in more detail below). **<u>Source of utility data:</u>** Utilities were elicited from a parallel valuation study, which analysed patient preference for GC relative to MVAC. A time trade-off (TTO) analysis was conducted. The authors considered it unethical to employ this analysis in patients with high mortality. They instead targeted healthcare professionals, specialising in medical oncology as the best patient approximation. The enrolment criteria were: • Educational qualifications for specialist medical			**Total costs:** ***Incremental cost (based on upper estimate of bias corrected 68.4% CI)*** **ICER (cost per QALY):** **<u>Favourable confidence interval limit</u>** **Effectiveness:** Willingness to trade time (WTTT) Utility gain on treatment ***Utility gain over life expectancy*** **Total costs:** ***Incremental cost (based on lower estimate of bias corrected 68.4% CI)*** **ICER (cost per QALY):** **<u>Uncertainty:</u>** One-way sensitivity analyses were conducted on various cost variables. The authors tested sensitivity by applying values 25% higher and lower than the original unit cost. Since the results were found to be symmetrical, the authors only deemed it necessary to present one set of results (upper cost estimates).	 ***£3,526*** ***£33,589*** 36.78 weeks 0.613 ***0.188 QALYs*** ***£2,427*** ***£12,911***	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	oncology nursing/clinician level • Employed currently, or within the last 6 months in a medical oncology treatment facility • At least 2 years experience of working in medical oncology The analysis involved the calculation of utilities expressed as a willingness-to-trade time (WTTT), through evaluation of individual treatment features. Specifically, the study values the superior toxicity profile of GC given comparable survival data. The results allowed for the estimation of utility gains associated with GC over MVAC. It was conservatively assumed that this incremental utility gain only applied to the period of time that patients received chemotherapy (mean duration of 18.4 weeks). Thereafter, there was no difference in			The results of the one-way sensitivity analyses conducted on costs were: • Unit costs of inpatient chemotherapy administration + 25% • Unit costs of outpatient chemotherapy administration + 25% • Cost per day of treatment for febrile neutropenia + 25% • Cost per day of treatment for anemia + 25% • Cost per day of treatment for fever + 25% • Cost per day of treatment for hypomagnesaemia + 25% • Cost per day of treatment for leucopoenia + 25% • Cost per day of treatment for nausea and vomiting + 25% • Cost per day of treatment for thrombocytopenia + 25% • Cost per day of treatment for other adverse events + 25% The authors state that they also performed one-way sensitivity tests on the length of stay associated with each adverse event and inpatient chemotherapy administration.	**ICER result (change from baseline value)** £23,619 (+£694) £24,228 (+£1,303) £22,400 (-£525) £22,889 (-£36) £22,796 (-£129) £22,924 (-£1) £22,900 (-£25) £22,827 (-£98) £22,971 (+£46) £22,731 (-£194)	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	quality of life between the two groups. **<u>Source of cost data:</u>** A cost analysis was performed based on the phase III clinical trial described above. A mean total cost per patient was calculated for patients in each treatment arm by combining medical resource use data in the trial with UK unit costs. The following resources were included in the costing study: • Study medication • Administration of study medication (inpatient and outpatient) • Hospitilisations • Healthcare professional visits outside of protocol events • Medical procedures outside of protocol events • Blood transfusion • Concomitant medications UK unit costs were primarily			However, the authors did not consider it necessary to present these results as they produced identical results to those already presented. The authors concluded that the model was robust to changes in variations to unit cost and length of stay. The authors considered the uncertainty shown in the CI calculations presented above to be the only major source of uncertainty in the model. Probabilistic sensitivity analysis (PSA) was not considered by the authors. However, the method used in the bootstrapping of cost estimates appears to be similar to a PSA methodology.		

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	sourced from the British National Formulary (BNF 41) and NHS reference costs. The costs of some concomitant medications were sourced from the pharmaceutical companies that manufacture them. The authors conducted bias-corrected bootstrapping to estimate the distribution of the mean cost per patient in each treatment arm. **Currency unit:** UK pound sterling (£) **Cost year:** 2001 **Discounting:** No discounting was performed as it was not considered necessary given short time horizon.					

5.1.2 Post-first line chemotherapy

Review question: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

Rationale

First line chemotherapy for metastatic disease is widely accepted as appropriate treatment for at least a proportion of patients.

Management of patients who progress on or relapse after 1st line treatment is much more controversial. Prognosis is poor with median survivals measured in a few months. There is a wide variety of practice in whether to offer 2nd line therapy to such patients. It is likely response rates are less; and toxicity may be higher thus questioning the clinical benefits of treatment. A key question is first therefore whether there is a role for further chemotherapy in some or all patients? If so can we identify the patients that are most likely to benefit and/or those in which chemotherapy is ineffective and treatment be avoided.

If patients are thought suitable for chemotherapy what form should this be? Should patients be re-challenged with initial chemotherapy or alternative combination regime (eg MVAC if Gemcitabine/cisplatin) was used first. Are other alternatives likely to be as effective (eg Paclitaxel) even though not licensed? Are single drugs better or worse option than combination?

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with incurable locally advanced or metastatic bladder cancer that has progressed following first line chemotherapy	Chemotherapy agents for second-line chemotherapy (alone or in combination): Paclitaxel, Irinotecan, Bortezomib, Pemetrexed, Oxaliplatin, Ifosfamide, Lapatinib, Docetaxel, Gemcitabine, Topotecan, Carboplatin, Gefitinib, Sorafenib, Sunitinib, MVAC (vinflunine for search)	Each other best supportive care	• Overall survival • Progression free survival • Treatment-related mortality • Treatment related morbidity • Health-related quality of life, inc patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. Randomised trials and single-arm phase II studies were selected for this review question.

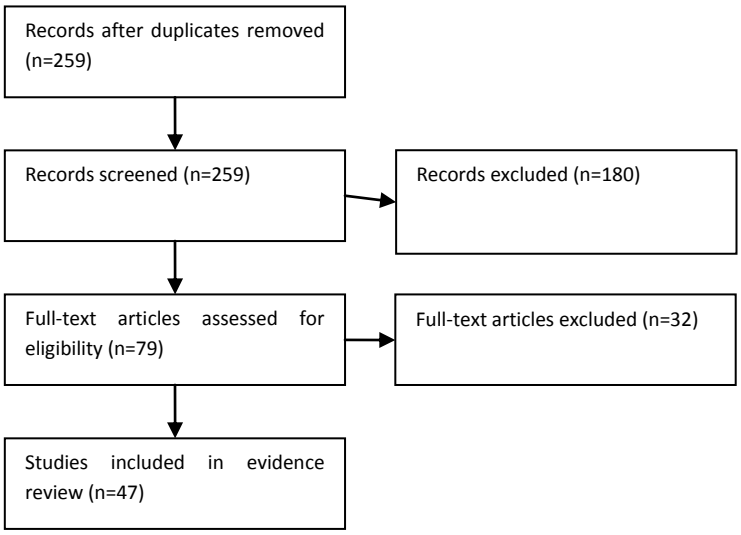
Data synthesis

Data from comparative studies were extracted into RevMan and risk ratios were calculated where possible.

RESULTS

Result of the literature searches

Figure 74. Study flow diagram



Study quality and results

The included evidence is summarised in Tables 140-170.

Evidence statements

Single-agent chemotherapy

Very low quality evidence for Topotecan, Iritonecan, Lapatanib, Sorefanib, Oxaliplatin and Sunitinib was provided by one non-comparative phase II study for each regimen. Overall survival ranged from 4.2 months (Lapatanib) to 7.1 months (Sunitinib). Progression-free survival ranged from 1.5 months (Topotecan) to 2.4 months (Sunitinib). Overall tumour response rate was highest for Topotecan at 9%. Toxicity rates were highest for Topotecan with 43%, 61%, and 77% of participants developing grade 3-4 thrombocytopenia, anaemia, and leucopenia, respectively. Two studies (46 participants) provided very low quality evidence on Bortezomib, with median overall survival durations of 3.5 months (Gomez-Aubin et al., 2007) and 5.7 months (Rosenberg et al., 2008). Both studies were closed early due to a lack of tumour response to the treatment, with no responses reported in either study. One study (47 participants) provided very low quality evidence of Pemetrexed, with a median overall survival of 9.2 months and a response rate of 28% for those previously treated in the metastatic setting (Sweeny et al., 2006). A second smaller study (13 participants) of Pemetrexed reported a lower response rate of 8% (Galsky et al., 2007). Across both studies, 12% of participants reported grade 3-4 neutropenia and thrombocytopenia. Very low quality evidence for Gemcitabine was provided by four studies (133

participants), with overall survival ranging from 5 months to 13 months across studies and an overall tumour response of 22%. Grade 3-4 neutropenia was the most common adverse event (37% of participants) (2 studies, 79 participants). In one study (Albers et al., 2002), 25 participants reported health-related quality of life, where responders to Gemcitabine showed an improvement in pain score from 4.3 to 5.8 on a 7-point scale. In contrast, non-responders reported an increase in pain during treatment.

Multi-agent chemotherapy

The combination of Gemcitabine and Paclitaxel (GP) was reported by 6 studies (109 participants, very low quality evidence). The overall response rate was 30%, with median overall survival ranging from 8 months to 12.4 months. One study reported a median progression-free survival of 6.1 months (Ikeda et al., 2011). Four studies reported grade 3-4 neutropenia, with an overall rate of 42%. One randomised phase III trial (Albers et al., 2011) and one randomised phase II trial (Fechner et al., 2006) provided low quality evidence of short-term (three-week schedule) versus prolonged (maintenance until progression) GP regimes (123 participants). No differences in overall survival and progression-free survival were reported between trial arms. In the phase III trial median overall survival was 7.8 months in the subgroup of patients who had first-line chemotherapy for metastatic cancer (Albers et al., 2011). The pooled overall tumour response rate was 41% in both trial arms. Grade 3-4 leucopenia was the most common toxicity with no difference in rate between short-term and maintenance GP treatment (36% versus 23%). Two treatment-related deaths were reported on the prolonged GP arm in the phase III study. Several small non-randomised studies providing very low quality evidence, generally show that other non-platinum based regimens (e.g. Methotrexate & Paclitaxel; Paclitaxel & Ifosfamide; Docetaxel & Ifosfamide; Docetaxel & Oxaliplatin; Gemcitabine & Ifosfamide; Gemcitabine & Docetaxel) have lower response rates and overall survival durations than Gemcitabine and Paclitaxel.

Three studies (93 participants) reported very low quality evidence about Carboplatin and Paclitaxel, with median overall survival ranging from six to 11 months, and an overall response rate of 25%. Progression-free survival was around four months in all three studies. Grade 3-4 neutropenia was reported in 50 out of 93 (54%) participants. Health-related quality of life was reported by one study, where there were no differences between pre-treatment and post-treatment scores on the EORTC-QLQ C30. Cisplatin based multi-agent chemotherapy regimens (MVAC; Gemcitabine & Cisplatin (GC); Paclitaxel, Methotrexate & Cisplatin (PMC); Paclitaxel & Cisplatin; Cisplatin, Gemcitabine & Ifosfamide) produced response rates of 30% to 40% and overall survival durations of 9.5 to 11 months (very low quality evidence). Rates of grade 3-4 neutropenia were 30%-67% and rates of grade 3-4 thrombocytopenia were 30%-32% for MVAC, GC and PMC. Lower toxicity rates were reported for the regimen of Paclitaxel & Cisplatin, with 5% grade 3-4 neutropenia and 1% grade 3-4 thrombocytopenia and anaemia (Uhm et al., 2007). One study (26 participants, very low quality evidence) reported a median overall survival and progression-free survival of 12.6 months and 5 months with Gemcitabine, Carboplatin & Docetaxel (Tsuruta et al., 2011). Excluding those who had received combination radiation therapy, the overall tumour response rate was 56%. Toxicity data was not reported separately for patients receiving second-line chemotherapy. Grade 3-4 neutropenia was reported in 80% of participants, thrombocytopenia in 51%, and anaemia in 43%. There were no treatment-related deaths.

Best supportive care

Moderate quality evidence from the control arm of a phase III randomised trial reported a median overall survival of 4.6 months and a median progression-free survival of 1.5 months for 117 participants receiving best supportive care for progression after first-line chemotherapy (Bellmunt et al., 2009). There were no tumour responses. One patient reported grade 3-4 neutropenia and one patient reported grade 3-4 thrombocytopenia. Nine participants reported grade 3-4 anaemia. Health-related quality of life as measured by the EORTC QLQ-C30, decreased continuously from baseline through to week 18 (mean scores were not reported).

Table 140. GRADE evidence profile: Topotecan for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topotecan	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=44	-	Median OS=6.3 months		⊕OOO VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=44	-	Median PFS=1.5 months		⊕OOO VERY LOW
Overall tumour response (assessed with: ECOG criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	4/44[3] (9.1%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia											
0[1]	No evidence available										
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	19/44 (43.2%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	27/44 (61.4%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	34/44 (77.3%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	0/44 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Witte 1998; [2] Small sample size and low number of events limits the precision of this outcome; [3] All partial responses, no complete responses

Table 141. GRADE evidence profile: Iritonecan for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iritonecan	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=40	-	Median OS=5.4 months		⊕OOO VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=40	-	Median PFS=2.1 months		⊕OOO VERY LOW
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	none	serious[2]	none	2/40 (5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia											
1[1]	observational studies	none	none	none	serious[2]	none	7/40 (17.5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia											
1[1]	observational studies	none	none	none	serious[2]	none	2/40 (5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia											
1[1]	observational studies	none	none	none	serious[2]	none	2/40 (5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia											
1[1]	observational studies	none	none	none	serious[2]	none	5/40 (12.5%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	0/40 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Beer 2008; [2] Small sample size and low number of events limits the precision of this outcome

Table 142. GRADE evidence profile: Lapatanib for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lapatanib	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=59	-	Median OS=4.2 months		⊕OOO VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=59	-	Median PFS=2 months		⊕OOO VERY LOW
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	none	serious[2]	none	1/59 (1.7%)	-	-	-	⊕OOO VERY LOW
Any adverse event (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	54/59 (91.5%)[3]	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	5/59 (8.5%)[4]	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Wulfing 2009; [2] Small sample size and low number of events limit the precision of this outcome; [3] The most common grade 3 and/or 4 adverse events were vomiting (7%), diarrhoea (3%), dehydration (3%), and hyponatremia (3%); [4] Five patients died from serious adverse events: febrile neutropenia, cardiac arrest, enterostomy suture leakage, metastatic neoplasm, exacerbated dyspnea

Table 143. GRADE evidence profile: Bortezomib for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bortezomib	Control	Relative (95% CI)	Absolute	
Overall survival											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	N=46	-	Median OS = 3.5 and 5.7 months		⊕OOO VERY LOW
Progression-free survival											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	N=46	-	Median PFS = 1.4 and 2 months		⊕OOO VERY LOW
Overall tumour response (assessed with: RECIST)											
2[1]	observational studies	none	none	serious[2]	none	none	0/46 (0%)	-	-	-	
Grade 3-4 Neutropenia (assessed with: NCI-CTCAE)											
1[4]	observational studies	none	none	none	serious[3]	none	0/24 (0%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	1/46 (2.2%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	2/46 (4.3%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTCAE)											
1[4]	observational studies	none	none	none	serious[3]	none	0/24 (0%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
0[1]	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Rosenberg 2008, Gomez-Abuin 2007

[2] Adjuvant and neoadjuvant chemotherapy considered as first-line therapy in Gomez-Abuin 2007 (40% of sample)

[3] Small sample size limits the precision of this outcome

[4] Rosenberg 2008

Table 144. GRADE evidence profile: Sorafenib for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sorafenib	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=22	-	Median OS=6.8 months		⊕OOO VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=22	-	Median PFS=2.2 months		⊕OOO VERY LOW
Overall tumour response (assessed with: RECIST)											
1	observational studies	none	none	none	serious[2]	none	0/22 (0%)	-	-	-	⊕OOO VERY LOW
Toxicity (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	0/22 (0%)[3]	-	-	-	⊕OOO VERY LOW
Grade 4 pulmonary embolism (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	2/22 (9.1%)	-	-	-	⊕OOO VERY LOW
Grade 3 fatigue (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	5/22 (22.7%)	-	-	-	⊕OOO VERY LOW
Grade 3 hand-foot reaction (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	5/22 (22.7%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	0/22 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Dreicer 2009

[2] Small sample size and low number of events limit precision of outcome

[3] Toxicity data not fully reported. Authors state that "Toxicity from sorafenib was similar to that seen in a renal cancer population".

Table 145. GRADE evidence profile: Oxaliplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxaliplatin	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=20	-	Median OS=7 months		⊕OOO VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=20	-	Median PFS=1.5 months		⊕OOO VERY LOW
Overall tumour response (assessed with: WHO criteria)											
1[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	1/20 (5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Haematological toxicity (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	0/22 (0%)[3]	-	-	-	⊕OOO VERY LOW
Grade 3 Fatigue (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	4/20 (20%)	-	-	-	⊕OOO VERY LOW
Grade 3 Nausea (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	2/20 (10%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	1/20 (5%)[4]	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Winquist 2005

[2] Small sample size and low number of events limits the precision of this outcome

[3] No haematological toxicity above grade 2 was seen. No symptomatic neutropenia.

[4] One treatment-related death from pulmonary embolism

Table 146. GRADE evidence profile: Pemetrexed for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pemetrexed	Control	Relative (95% CI)	Absolute	
Overall survival (follow-up median 9.2 months)											
1[1]	observational studies	none	none	none[2]	serious[3]	none	N=29	-	Median OS = 9.2 months		⊕OOO VERY LOW
Progression-free survival (follow-up median 9.2 months)											
1[1]	observational studies	none	none	serious[4]	serious[3]	none	N=47	-	Median PFS = 2.9 months		⊕OOO VERY LOW
Overall tumour response (assessed with: SWOG / RECIST criteria)											
2[5]	observational studies	none	none	serious[6]	serious[3]	none	9/41 (22%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
2[5]	observational studies	none	none	serious[4]	serious[3]	none	7/60 (11.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
2[5]	observational studies	none	none	serious[4]	serious[3]	none	7/60 (11.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
2[5]	observational studies	none	none	serious[4]	serious[3]	none	4/60 (6.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia											
1[1]	observational studies	none	none	serious[4]	serious[3]	none	1/47 (2.1%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
2[5]	observational studies	none	none	serious[4]	serious[3]	none	0/60 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Sweeny 2006; [2] Neoadjuvant and adjuvant chemotherapy considered as first-line therapy. Median overall survival was reported separately for patients treated in the metastatic setting (n=29)
[3] Small sample size/low number of events limits the precision of this outcome; [4] Progression-free survival and toxicity was not reported separately for patients who received prior neoadjuvant/adjuvant chemotherapy and those treated in the metastatic setting
[5] Galsky 2007, Sweeny 2006; [6] Tumour response was not reported separately for patients who received prior neoadjuvant/adjuvant chemotherapy and those treated in the metastatic setting in Galsky 2007

Table 147. GRADE evidence profile: Docetaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Docetaxel	Control	Relative (95% CI)	Absolute	
Overall survival											
2[1]	observational studies	none	none	serious[2]	serious[5]	none	N=102	-	Median OS =9 and 7.3 months		⊕OOO VERY LOW
Progression-free survival											
1[3]	observational studies	none	none	serious[2]	serious[5]	none	N=72	-	Median PFS = 1.58 months		⊕OOO VERY LOW
Overall tumour response											
2[1]	observational studies	none	none	serious[2]	serious[5]	none	12/102 (11.8%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
2[1]	observational studies	none	none	serious[2]	serious[5]	none	35/102 (34.3%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[4]	observational studies	none	none	serious[2]	serious[5]	none	1/30 (3.3%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
2	observational studies	none	none	serious[2]	serious[5]	none	9/102 (8.8%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia											
0	No evidence available										
Treatment-related mortality											
1[3]	observational studies	none	none	serious[2]	serious[5]	none	0/72 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Choueiri 2012, McCaffrey 1997; [2] Neoadjuvant and adjuvant chemotherapy considered as first-line chemotherapy in both studies

[3] Choueiri 2012; [4] McCaffrey 1997

[5] Small sample size/low number of events limits the precision of this outcome

Table 148. GRADE evidence profile: Ifosfamide for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ifosfamide	Control	Relative (95% CI)	Absolute	
Overall survival											
2[1]	observational studies	none	none	none	serious[2]	none	N=86	-	Median OS = 8 and 5.5 months		⊕OOO VERY LOW
Progression-free survival											
2[1]	observational studies	none	none	none	serious[2]	none	N=86	-	Median PFS = 6 and 2.5 months		⊕OOO VERY LOW
Overall tumour response (assessed with: ECOG/WHO criteria)											
2[1]	observational studies	none	none	none	serious[2]	none	12/76 (15.8%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia											
0	No evidence available										
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[3]	observational studies	none	none	none	serious[2]	none	12/56 (21.4%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[2]	observational studies	none	none	none	serious[2]	none	23/56 (41.1%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia											
1[2]	observational studies	none	none	none	serious[2]	none	36/56 (64.3%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
2[1]	observational studies	none	none	none	serious[2]	none	4/76 (5.3%)[4]	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Pronzato 1997, Witte 1997; [2] Small sample size/low number of events limits the precision of this outcome

[3] Witte 1997 (no grade 3-4 hematologic toxicities were reported by Pronzato (1997) which may be due to differences in the dosing schedule of Ifosfamide used, therefore toxicity data was not pooled); [4] Four early deaths were reported by Witte 1997, which although could not be directly linked to treatment, it was assumed treatment was a contributing factor

Table 149. GRADE evidence profile: Sunitinib for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sunitinib Cohort A	Sunitinib Cohort B	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=45	N=32	Median OS = 7.1 vs. 6.0 months (p=0.4)		⊕OOO VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=45	N=32	Median PFS = 2.4 vs.2.3 months (p=0.4)		⊕OOO VERY LOW
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	3/45 (6.7%)	1/32 (3.1%)	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/45 (2.2%)	3/32 (9.4%)	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	9/45 (20%)	3/32 (9.4%)	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	7/45 (15.6%)	4/32 (12.5%)	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	2/45 (4.4%)	3/32 (9.4%)	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/45 (2.2%)	0/32 (0%)	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Gallagher 2010; [2] Neoadjuvant and adjuvant chemotherapy (39% of sample) considered as first-line chemotherapy

[3] Small sample size/low number of events limits the precision of this outcome

Table 150. GRADE evidence profile: Paclitaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paclitaxel	Control	Relative (95% CI)	Absolute	
Overall survival											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	N=76	-	Median OS = 7.2 and 6.5 months		⊕OOO VERY LOW
Progression-free survival											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	N= 76	-	Median PFS = 2.2 and 3 months		⊕OOO VERY LOW
Overall tumour response (assessed with: RECIST)											
2[4]	observational studies	none	none	serious[2]	serious[3]	none	7/76 (9.2%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
2[5]	observational studies	none	none	serious[2]	serious[3]	none	3/74 (4.1%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[6]	observational studies	none	none	serious[2]	serious[3]	none	0/30 (0%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	9/74 (12.2%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life (assessed with: Improvement in at least 1 domain (≥+5 points) FACT-G, FACT bl, FACT-Taxane)											
1[7]	observational studies	none	none	serious[2]	serious[3]	none	6/35 (17.1%)[8]	-	-	-	⊕OOO VERY LOW

[1] Vaughn 2002, Joly 2009; [2] Neoadjuvant and adjuvant chemotherapy considered as first-line chemotherapy; [3] Small sample size/low number of events suggest imprecise outcome

[4] Vaughn 2002, Joly 2009. Papamichael 1997 was not included in the pooled analysis due to different dosage schedules used. Overall response rate reported by Papamichael was 4/14 (29%) compared to 9% (Joly, 2009) and 10% (Vaughn, 2002)

[5] Vaughn 2002, Joly 2009. Papamichael 1997 was not included in the pooled analysis due to different dosage schedules used and toxicity data was not reported consistently. Papamichael reported that grade 3-4 hematologic toxicity was seen in 23/42 (55%) courses; [6] Vaughn 2002; [7] Joly 2009; [8] There was no decrease in the different QoL domains during chemotherapy

Table 151. GRADE evidence profile: Gemcitabine for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine	Control	Relative (95% CI)	Absolute	
Overall survival											
4[1]	observational studies	none	none	serious[2]	serious[8]	none	N=133 [3]	-	-	-	⊕OOO VERY LOW
Progression-free survival											
3[4]	observational studies	none	none	serious[2]	serious[8]	none	N=119 [5]	-	-	-	⊕OOO VERY LOW
Overall tumour response (assessed with: WHO criteria)											
4[1]	observational studies	none	none	serious[2]	serious[8]	none	28/127 (22%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia											
2[6]	observational studies	none	none	serious[2]	serious[8]	none	29/79 (36.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia											
4[1]	observational studies	none	none	serious[2]	serious[8]	none	11/131 (8.4%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia											
4[1]	observational studies	none	none	serious[2]	serious[8]	none	16/131 (12.2%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia											
4[1]	observational studies	none	none	serious[2]	serious[8]	none	29/131 (22.1%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[7]	observational studies	none	none	serious[2]	serious[8]	none	0/44 (0%)	-	-	-	
Health-related quality of life (measured with: Spitzer pain index; Better indicated by lower values)											
1[9]	observational studies	none	none	serious[2]	serious[8]	none	25[10]	-	-		⊕OOO VERY LOW

[1] Lorusso 1998, Albers 2002, Gebbia 1999, Akaza 2007; [2] Adjuvant and neoadjuvant chemotherapy considered as first-line chemotherapy; [3] Median overall survival ranged from 5 months to 13 months across studies; [4] Lorusso 1998, Albers 2002, Akaza 2007; [5] Median progression-free survival ranged from 3.1 months to 4.9 months; [6] Lorusso 1997, Akaza 2007; [7] Akaza 2007
[8] Small sample size and/or low number of events limit the precision of this outcome; [9] Albers 2002; [10] Non-responders showed a decrease in pain values from 5.3 to 4.8 which corresponds to an increase in pain during treatment. Responders showed an improvement in pain values from 4.3 to 5.8 ($p<0.05$).

Table 152. GRADE evidence profile: Gemcitabine & Paclitaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine, paclitaxel	Control	Relative (95% CI)	Absolute	
Overall survival											
4[1]	observational studies	none	none	none	serious[13]	none	N=92 [2]	-	-	-	⊕OOO VERY LOW
Progression-free survival (follow-up median 20.4 months)											
1[3]	observational studies	none	none	serious[4]	serious[13]	none	N=24 [5]	-	-	-	⊕OOO VERY LOW
Overall tumour response (assessed with: RECIST/WHO criteria)											
6[6]	observational studies	none	none	none	serious[13]	none	33/109 (30.3%)[7]	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
4[1]	observational studies	none	none	none	serious[13]	none	50/118 (42.4%)[8]	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
4[1]	observational studies	none	none	none	serious[13]	none	10/92 (10.9%)[9]	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
3[10]	observational studies	none	none	none	serious[13]	none	5/68 (7.4%)[11]	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia											
0	No evidence available										
Treatment-related mortality											
4[1]	observational studies	none	none	none	serious[13]	none	1/92 (1.1%)[12]	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Sternberg 2001, Kanai 2008, Suyama 2009, Ikeda 2011; [2] Median overall survival reported were 8 months (Sternberg 2001), 11.3 months (Suyama 2009),11.5 months (Kanai 2008), and 12.4 months (Ikeda, 2011). Takahashi (2006) reported a median overall survival of 12.1 months, but this included patients receiving both first-line and second-line GP chemotherapy; [3] Ikeda 2011
[4] Neoadjuvant and adjuvant chemotherapy considered first-line therapy. Proportion of participants not reported; [5] Median progression-free survival was 6.1 months; [6] Kaufman 2000, Sternberg 2001, Takahashi 2006, Kanai 2008, Suyama 2009, Ikeda 2011; [7] Overall tumour response rate ranged from 17% to 42% across studies; [8] Rate of grade 3-4 neutropenia ranged from 30% to 67% across studies; [9] Rates of grade 3-4 thrombocytopenia ranged from 0% to 29% across studies; [10] Sternberg 2001, Kanai 2008, Suyama 2009; [11] Rates of grade 3-4 anaemia ranged from 0% to 15%
[12] One treatment related death reported by Sternberg 2001; [13] Small sample size/low number of events reduces precision

Table 153. GRADE evidence profile: Short-term versus prolonged gemcitabine and paclitaxel

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-term GP	Prolonged GP	Relative (95% CI)	Absolute	
Overall survival (mortality rate, minimum follow-up 5 years)											
1[1]	randomised trials	none	none	serious[2]	serious[5]	none	47/48 (97.9%)	46/48 (95.8%)	HR 0.94 (0.63 to 1.41)[3]	Median OS, 7.8 vs. 8 months	⊕⊕OO LOW
Progression-free survival											
2[7]	randomised trials	none	none	serious[2]	serious[5]	none	N=62	N=61	Unable to calculate HR[4]	-	⊕⊕OO LOW
Overall tumour response (assessed with: RECIST criteria)											
2[7]	randomised trials	none	none	serious[2]	serious[5]	none	22/54 (40.7%)	22/54 (40.7%)	RR 1.00 (0.63 to 1.58)	0 fewer per 1000 (from 151 fewer to 236 more)	⊕⊕OO LOW
Grade 3-4 Thrombocytopenia (assessed with: WHO criteria)											
1[6]	randomised trials	none	none	serious[2]	serious[5]	none	0/14 (0%)	2/13 (15.4%)	RR 0.13 (0.01 to 2.36)	134 fewer per 1000 (from 152 fewer to 209 more)	⊕⊕OO LOW
Grade 3-4 Anaemia (assessed with: WHO/NCI criteria)											
2[7]	randomised trials	none	none	serious[2]	serious[5]	none	5/54 (9.3%)	14/54 (25.9%)	RR 0.42 (0.17 to 1.03)	150 fewer per 1000 (from 215 fewer to 8 more)	⊕⊕OO LOW
Grade 3-4 Leucopenia (assessed with: WHO criteria)											
1[6]	randomised trials	none	none	serious[2]	serious[5]	none	5/14 (35.7%)	3/13 (23.1%)	RR 1.55 (0.46 to 5.22)	127 more per 1000 (from 125 fewer to 974 more)	⊕⊕OO LOW
Treatment-related mortality											
1[1]	randomised trials	none	none	serious[2]	serious[5]	none	0/40 (0%)	2/41 (4.9%)	RR 0.20 (0.01 to 4.14)	39 fewer per 1000 (from 48 fewer to 153 more)	⊕⊕OO LOW
Health-related quality of life											
0	No evidence available					none	-	-	-	-	

[1] Albers 2011; [2] Adjuvant and neoadjuvant chemotherapy considered as first-line chemotherapy (56% of sample in Albers 2011, 67% of sample in Fechner 2006); [3] HR calculated from Albers (2011). Insufficient data from Fechner (2006). Median overall survival was 13 months with short-term GP, and 9 months with prolonged GP (Fechner, 2006). Median OS was 7.8 months in the subgroup of patients who had first-line chemotherapy for metastatic cancer (Albers 2011); [4] No significant differences between trial arms were reported. Median progression-free survival was 11 months (Fechner 2006) and 4 months (Albers 2011) with short-term GP, and 6 months (Fechner 2006) and 3.1 months (Albers 2011) with prolonged GP; [5] Small sample size/low number of events and/or wide confidence intervals suggest imprecise outcome; [6] Fechner 2006; [7] Albers 2011; Fechner 2006

Table 154. GRADE evidence profile: Paclitaxel & Carboplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carboplatin, paclitaxel	Control	Relative (95% CI)	Absolute	
Overall survival											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	N=93[3]	-	-	-	⊕OOO VERY LOW
Progression-free survival											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	N=93[4]	-	-	-	⊕OOO VERY LOW
Overall tumour response (assessed with: RECIST/WHO criteria)											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	23/93 (24.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	50/93 (53.8%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	7/93 (7.5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	23/93 (24.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTC)											
1[5]	observational studies	none	none	serious[2]	serious[6]	none	16/44 (36.4%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
2[7]	observational studies	none	none	serious[2]	serious[6]	none	1/75 (1.3%)[8]	-	-	-	⊕OOO VERY LOW
Health-related quality of life (follow-up 3 months; assessed with: EORTC-QLQ C30)											
1[9]	observational studies	none	none	serious[2]	serious[6]	none	15[10]	-	-	-	⊕OOO VERY LOW

[1] Kuono 2007, Vaishampayan 2005, Soga 2007; [2] Neoadjuvant and adjuvant chemotherapy considered as first-line chemotherapy in all studies; [3] Median overall survival reported = 6 months, 7.9 months and 11 months (Vaishampayan 2005, Kuono 2007, Soga 2007); [4] Median progression-free survival = 3.7 months, 4 months and 4 months (Kuono 2007, Vaishampayan 2005, Soga 2007)
[5] Vaishampayan 2005; [6] Small sample size/low number of events limits the precision of this outcome; [7] Kuono 2007, Vaishampayan 2005; [8] One patient with a PS score of 3 died due to neutropenic sepsis (Kuono 2007). No further PS3 patients were recruited; [9] Soga 2007; [10] There were no differences between pre-treatment and post-treatment data on all scales of the EORTC QLQ C30

Table 155. GRADE evidence profile: Methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MVAC	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=30	-	Median OS = 10.9 months		⊕OOO VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=30	-	Median PFS = 5.3 months		⊕OOO VERY LOW
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	none	serious[2]	none	9/30 (30%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	19/30 (63.3%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	9/30 (30%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	5/30 (16.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Mucositis (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	4/30 (13.3%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	0/30 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Han 2008

[2] Small sample size/low number of events limits the precision of this outcome

Table 156. GRADE evidence profile: Gemcitabine, cisplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine, cisplatin	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=33	-	Median OS = 10.5 months		⊕OOO VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	13/33 (39.4%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	22/33 (66.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	10/33 (30.3%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	14/33 (42.4%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	15/33 (45.5%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/33 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Gondo 2011

[2] Adjuvant MVAC considered as first-line MVAC chemotherapy

[3] Small sample size/ low number of events limit the precision of this outcome

Table 157. GRADE evidence profile: Paclitaxel, cisplatin, methotrexate for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paclitaxel, methotrexate, cisplatin	Control	Relative (95% CI)	Absolute	
Overall survival											
0	No evidence available										
Progression-free survival											
0	No evidence available										
Overall tumour response											
1[1]	observational studies	none	none	none	serious[2]	none	10/25 (40%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: ECOG criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	9/25 (36%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: ECOG criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	8/25 (32%)	-	-	-	⊕OOO VERY LOW
Significant nephrotoxicity (assessed with: >50% serum creatinine increase)											
1[1]	observational studies	none	none	none	serious[2]	none	6/25 (24%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Tu 1995

[2] Small sample size/ low number of events limit the precision of this outcome

Table 158. GRADE evidence profile: Paclitaxel, cisplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paclitaxel, cisplatin	Control	Relative (95% CI)	Absolute	
Overall survival (follow-up median 16.4 months)											
1[1]	observational studies	none	none	none	serious[2]	none	N=28	-	Median OS = 10.3 months		⊕OOO VERY LOW
Progression-free survival (follow-up median 16.4 months)											
1[1]	observational studies	none	none	none	serious[2]	none	N=28	-	Median PFS = 6.2 months		⊕OOO VERY LOW
Overall tumour response (assessed with: WHO criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	10/28 (35.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	5/110 (4.5%)[3]	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	1/110 (0.91%)[3]	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[3]	none	1/110 (0.91%)[3]	-	-	-	⊕OOO VERY LOW
Grade 3-4 Emesis (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	10/28 (35.7%)[4]	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	0/28 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Uhm 2007

[2] Small sample size / low number of events limit the precision of this outcomes

[3] Toxicity rate reported per cycle of chemotherapy

[4] Toxicity rate reported per patient

Table 159. GRADE evidence profile: Methotrexate, paclitaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate, paclitaxel	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=20	-	Median OS = 5 months		⊕OOO VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	6/20 (30%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	3/20 (15%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/20 (0%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/20 (5%)	-	-	-	⊕OOO VERY LOW
Grade 3 Mucositis (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/20 (5%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/20 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available					none	-	-	-	-	

[1] Bellmunt 2002

[2] Neoadjuvant chemotherapy considered as first-line chemotherapy

[3] Small sample size / low number of events limit the precision of this outcome

Table 160. GRADE evidence profile: Paclitaxel, ifosfamide for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paclitaxel, ifosfamide	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=13	-	Median OS = 8 months		⊕OOO VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	2/13 (15.4%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	4/13 (30.8%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia											
1	observational studies	none	none	serious[2]	serious[3]	none	2/13 (15.4%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/13 (7.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia											
0	No evidence available										
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/13 (7.7%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Sweeny 1999

[2] Adjuvant and neoadjuvant chemotherapy considered as first-line chemotherapy (proportion of sample not stated)

[3] Small sample size/ low number of events limit the precision of this outcome

Table 161. GRADE evidence profile: Docetaxel, ifosfamide for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Docetaxel, ifosfamide	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=22	-	Median OS = 4 months		⊕OOO VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	5/20 (25%)	-	-	-	⊕OOO VERY LOW
Neutropenic sepsis (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/22 (4.5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/22 (4.5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/22 (0%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	11/53 (20.8%)[4]	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Krege 2001; [2] Neoadjuvant (n=2) and adjuvant (n=4) chemotherapy considered as first-line chemotherapy; [3] Small sample size / low number of events limit the precision of this outcome

[4] Reported as per cycle

Table 162. GRADE evidence profile: Docetaxel, oxaliplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Docetaxel, oxaliplatin	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=11	-	Median OS = 7 months		⊕OOO VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/11 (9.1%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/11 (0%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/11 (0%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/11 (0%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/11 (0%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/11 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Srinivas 2009; [2] Adjuvant chemotherapy considered as first-line chemotherapy (55% of sample); [3] Small sample size / low number of events limit the precision of this outcome. Trial stopped early due to low response to therapy.

Table 163. GRADE evidence profile: Cisplatin, Gemcitabine & Ifosfamide for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cisplatin, gemcitabine, ifosfamide	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=51	-	Median OS = 9.5 months		⊕OOO VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: complete or partial response for 2 months)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	20/49 (40.8%)	-	-	-	⊕OOO VERY LOW
Febrile Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	2/51 (3.9%)	-	-	-	⊕OOO VERY LOW
Dose limiting hematologic toxicity (assessed with: NCI-CTC - any grade 4 toxicity or persistent >grade 2 toxicity)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	48/51 (94.1%)[4]	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/51 (2%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Pagliaro 2002; [2] Adjuvant (20%) and neoadjuvant (4%) chemotherapy considered as first-line chemotherapy; [3] Small sample size / low number of events limit the precision of this outcome

[4] 100% dose omission on either day 8 or day 15 occured in virtually every course given, all due to granulocytopenia, thrombocytopenia or both

Table 164. GRADE evidence profile: Gemcitabine, Ifosfamide for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine, ifosfamide	Control	Relative (95% CI)	Absolute	
Overall survival											
2[1]	observational studies	none	none	none	serious[2]	none	N=57	-	Median OS = 4.8 and 9 months		⊕OOO VERY LOW
Progression-free survival											
2[1]	observational studies	none	none	none	serious[2]	none	N=57	-	Median PFS = 3.5 and 4 months		⊕OOO VERY LOW
Overall tumour response (assessed with: WHO criteria)											
2[1]	observational studies	none	none	none	serious[2]	none	12/57 (21.1%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: WHO criteria)											
1[3]	observational studies	none	none	none	serious[2]	none	9/34 (26.5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: WHO/ECOG criteria)											
2[1]	observational studies	none	none	none	serious[2]	none	12/57 (21.1%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: WHO/ECOG criteria)											
2[1]	observational studies	none	none	none	serious[2]	none	11/57 (19.3%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia (assessed with: ECOG criteria)											
1[4]	observational studies	none	none	none	serious[2]	none	10/23 (43.5%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[3]	observational studies	none	none	none	serious[2]	none	0/34 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Lin 2007, Pectasides 2001; [2] Small sample size / low number of events limit the precision of this outcome; [3] Pectasides 2001; [4] Lin 2007

Table 165. GRADE evidence profile: Gemcitabine, Docetaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine, docetaxel	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=29	-	Median OS = 7.7 months		⊕OOO VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: ECOG criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	5/27 (18.5%)	-	-	-	⊕OOO VERY LOW
Neutropenic fever											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	2/29 (6.9%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	4/29 (13.8%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	8/29 (27.6%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Granulocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	10/29 (34.5%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Dreicer 2003; [2] Adjuvant and neoadjuvant chemotherapy considered as first-line chemotherapy (proportion of sample not stated); [3] Small sample size / low number of events limit the precision of this outcome

Table 166. GRADE evidence profile: Gemcitabine, carboplatin, docetaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine, carboplatin, docetaxel	Control	Relative (95% CI)	Absolute	
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=26	-	Median OS = 12.6 months		⊕OOO VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=26	-	Median PFS = 5 months		⊕OOO VERY LOW
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	9/16 (56.3%)[4]	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2,5]	serious[3]	none	28/35 (80%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2,5]	serious[3]	none	18/35 (51.4%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2,5]	serious[3]	none	15/35 (42.9%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/35 (0%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Tsuruta 2011; [2] Neoadjuant and adjuvant chemotherapy considered as first-line chemotherapy; [3] Small sample size / low number of events limit the precision of this outcome

[4] Excluded participants who received combination radiation therapy; [5] Toxicity data not reported separately for 2nd line chemotherapy patients

Table 167. GRADE evidence profile: Methotrexate, Paclitaxel, Epirubicin, Carboplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MPEC	Control	Relative (95% CI)	Absolute	
Overall survival (median (range) follow-up: 14 (3-45) months)											
1[1]	observational studies	none	none	none	serious[2]	none	Median OS 12.5 months	-	-	-	⊕OOO VERY LOW
Progression-free survival (median (range) follow-up: 14 (3-45) months)											
1[1]	observational studies	none	none	none	serious[2]	none	Median PFS 12 months	-	-	-	⊕OOO VERY LOW
Overall tumour response rate (assessed with: WHO criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	15/38 (39.5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	12/40 (30%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	1/40 (2.5%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	2/40 (5%)	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Halim (2013)

[2] Low number of events/small sample size limits precision

Table 168. GRADE evidence profile: Best supportive care after progression from first-line chemotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Best supportive care	Control	Relative (95% CI)	Absolute	
Overall survival (mortality rate at follow-up)											
1[1]	randomised trials	none	none	none	serious[2]	none	103/117 (88%)	-	Median OS = 4.6 months		⊕⊕⊕O MODERATE
Progression-free survival											
1[1]	randomised trials	none	none	none	serious[2]	none	N=117	-	Median PFS = 1.5 months		⊕⊕⊕O MODERATE
Overall tumour response (assessed with: RECIST)											
1[1]	randomised trials	none	none	none	serious[2]	none	0/117 (0%)	-	-	-	⊕⊕⊕O MODERATE
Grade 3-4 Neutropenia (assessed with: NCI- CTC)											
1[1]	randomised trials	none	none	none	serious[2]	none	1/117 (0.85%)	-	-	-	⊕⊕⊕O MODERATE
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	none	serious[2]	none	1/117 (0.85%)	-	-	-	⊕⊕⊕O MODERATE
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	none	serious[2]	none	9/117 (7.7%)	-	-	-	⊕⊕⊕O MODERATE
Health-related quality of life											
1[1]	randomised trials	none	none	none	serious[2]	none	-[3]	-	-	-	⊕⊕⊕O MODERATE

[1] Bellmunt 2009; [2] Low number of events reduces precision of this outcome; [3] Mean scores not reported. There was a continuous decrement in quality of life scores from baseline through week 18. 24% receieved at least one palliative radiotherapy treatment

Table 169. Single-agent second-line chemotherapy trials in advanced bladder cancer

Trial	Regimen	N	Progression-free survival (months)	Median overall survival (months)	Overall Response rate	Complete response rate	Toxicity n (%) Grade 3-4				
							Neutropenia	Thrombocytopenia	Anaemia	Leucopenia	Toxic deaths
Witte 1998	Topotecan	44	1.5	6	4/44 (9%)	0/44		19/44 (43%)	27/44 (61%)	34/44 (77%)	1
Beer 2008	Iritonecan	40	2.1	5.4	2/40 (5%)	1/40	7/40 (18%)	2/40 (5%)	2/40 (5%)	5/40 (13%)	0
Wulfing 2009	Lapatinib	59	2	4.2	1/59 (2%)	0/59					5
Rosenberg 2008	Bortezomib	25	1.4	5.7	0/25	0/25	0/24	1/24 (4%)	2/24 (8%)		
Gomez-Abuin 2007	Bortezomib	21	2	3.5	0/21	0/21		0/21	0/21		
Dreicer 2009	Sorafenib	22	2.2	6.8	0/22	0/22					0
Winquist 2005	Oxaliplatin	20	1.5	7	1/20 (5%)	0/20	0	0	0	0	1
Sweeny 2006	Pemetrexed	47 (29)[8]	2.9 (NR)	9.6 (9.2)	13/47 (28%) (8/29, 28%)	3/47 (6%) (0/29, 0%)	4/47 9%	4/47 (9%)	1/47 (2%)	1/47 (2%)	0
Galsky 2007	Pemetrexed	13	NR	NR	1/12 (8%)	0/12	3/13 (23%)	3/13 (23%)	3/13 (23%)		0
McCaffrey 1997	Docetaxel	30	NR	9	4/30 (13%)	0/30	25/30 (83%)	1/30 (3%)	8/30 (27%)		
Choueiri 2012	Docetaxel (+ placebo)	72	1.58	7.03	8/72 (11%)	0/72	10/72 (14%)		1/72 (1%)		0
Pronzato 1997	Ifosfamide	20	6	8.0	1/20 (5%)	0/20		0/20	0/20	0/20	

[8] Number in brackets refers to those previously treated in the metastatic setting

Trial	Regimen	N	Progression-free survival (months)	Median overall survival (months)	Overall Response rate	Complete response rate	Toxicity n (%) Grade 3-4				
							Neutropenia	Thrombocytopenia	Anaemia	Leucopenia	Toxic deaths
Witte 1997	Ifosfamide	56	2.5	5.5	11/56 (20%)	5/56 (9%)		12/56 (21%)	23/56 (41%)	36/56 (64%)	4
Gallagher 2010	Sunitinib A Sunitinib B	45 32	2.4 2.3	7.1 6.0	3/45 (7%) 1/32(3%)	0 0	1/45 (2%) 3/32 (9%)	9/45 (20%) 3/32 (9%)	7/45 (16%) 4/32 (13%)	2/45 (4%) 3/32 (9%)	1
Vaughn 2002	Paclitaxel	31	2.2	7.2	3/31 (10%)	0/31	0/30	0/30	4/30 (13%)		
Papamichael 1997	Paclitaxel	14	NR	NR	4/14 (29%)	1/14 (7%)	Grade 3-4 hematologic toxicity seen in 23/42 courses. 2 neutropenic sepsis.				
Joly 2009	Paclitaxel	45	3	6.5	4/45 (9%)	1/45 (2%)	3/44 (6%)		5/44 (11%)		
Lorusso 1998	Gemcitabine	35	3.8	5	7/31 (23%)	4/31 (13%)	7/35 (20%)	5/35 (14%)	8/35 (23%)	4/35 (11%)	
Albers 2002	Gemcitabine	30	4.9	8.7	3/28 (11%)			3/28 (11%)	3/28 (11%)	10/28 (36%)	
Gebbia 1999	Gemcitabine	24	NR	13.0	7/24 (29%)	1/24 (4%)		0/24	0/24	3/24 (13%)	
Akaza 2007	Gemcitabine	44	3.1	12.6	11/44 (25%)	0/44	22/44 (50%)	3/44 (7%)	5/44 (11%)	9/44 (21%)	0
Bellmunt 2009	Best supportive care	117	1.5	4.6	0/117		1/117 (0/9%)	1/117 (0.9%)	9/117 (8%)		

Table 170. Multi-agent second-line trials in advanced bladder cancer

Trial	Regimen	N	Progression-free survival (months)	Median overall survival (months)	Overall response rate	Complete response rate	Toxicity Grade 3-4				
							Neutropenia	Thrombocytopenia	Anaemia	Leucopenia	Toxic deaths
Kaufman 2000	Gemcitabine, paclitaxel	6		NR	1/6 (17%)	1/6 (17%)	Not reported separately for 2nd line patients				
Sternberg 2001	Gemcitabine, paclitaxel	15		8	4/15 (27%)		13/41 (32%)	0/41	0/41		1
Kanai 2008	Gemcitabine, paclitaxel	20		11.5	6/20 (30%)	1/20 (5%)	6/20 (30%)	1/20 (5%)	3/20 (15%)		0
Suyama 2009	Gemcitabine, paclitaxel	33		11.3	10/30 (33%)	1/30 (3%)	15/33 (45%)	2/33 (6%)	2/33 (6%)		0
Ikeda 2011	Gemcitabine, paclitaxel	24	6.1	12.4	10/24 (42%)	2/24 (8%)	16/24 (67%)	7/24 (29%)			0
Takahashi 2006	Gemcitabine, paclitaxel	14		12.1 (all ps)	2/14 (14%)	0/14	Not reported separately for 2nd line patients				
Fechner 2006	Short-term Gem, paclitaxel Prolonged Gem, paclitaxel	30	11 6	13 9	7/14 (50%) 5/13 (39%)	7/14 (50%) 1/13 (8%)		0/14 (0%) 2/13 (15%)	3/14 (21%) 3/13 (23%)	5/14 (36%) 3/13 (23%)	
Albers 2011	Short-term Gem, paclitaxel Prolonged Gem, paclitaxel	48 48	4.0 3.1	7.8 8.0	15/40 (38%) 17/41 (42%)	5/40 (13%) 6/41 (15%)			3/40 (8%) 11/41 (27%)		0 2
Kuono 2007	Carboplatin, paclitaxel	31	3.7	7.9	10/31 (32%)	2/31 (6%)	18/31 (58%)	0/31	11/31 (35%)		1 (PS 3)

Trial	Regimen	N	Progression-free survival (months)	Median overall survival (months)	Overall response rate	Complete response rate	Toxicity Grade 3-4				
							Neutropenia	Thrombocytopenia	Anaemia	Leucopenia	Toxic deaths
Vaishampayan 2005	Carboplatin, paclitaxel	44	4	6	7/44 (16%)	1/44 (2%)	23/44 (52%)	4/44 (9%)	7/44 (16%)	16/44 (36%)	0
Soga 2007	Carboplatin, paclitaxel	18	4	11	6/18 (33%)	0/18	9/18 (50%)	3/18 (22%)	5/18 (28%)		
Halim 2013	Methotrexate, paclitaxel, epirubicin, carboplatin	38	12	12.5	15/38 (39.5%)	1/38 (3%)	12 (30%)	1 (2.5%)	2 (5%)		
Han 2008	MVAC	30	5.3	10.9	9/30 (30%)	2/30 (7%)	19/30 (63%)	9/30 (30%)	5/30 (17%)		0
Gondo 2011	Gemcitabine, Cisplatin	33		10.5	13/33 (39%)	2/33 (6%)	22/33 (67%)	10/33 (30%)	14/33 (42%)	15/33 (45%)	0
Tu 1995	Paclitaxel, methotrexate, cisplatin	25		NR	10/25 (40%)	0/25	9/25 (36%)	8/25 (32%)			
Uhm 2007	Paclitaxel, cisplatin	28	6.2	10.3	10/28 (36%)	3/28 (11%)	5/110 (5%) cycles	1/110 (1%)	1/110 (1%)		
Bellmunt 2002	Methotrexate, paclitaxel	20		5	6/20 (30%)		3/20 (15%)	0/20	1/20 (5%)		0
Sweeny 1999	Paclitaxel, ifosfamide	13		8	2/13 (15%)	2/13 (15%)	4/13 (34%)	2/13 (15%)	1/13 (8%)		
Krege 2001	Docetaxel, ifosphamide	22		4	5/20 (25%)	4/20 (20%)		1/53 (2%)	0/20	11/53 (21%)	
Srinivas 2009	Docetaxel, oxaliplatin	11		7	1/11 (9%)	0/11					0
Pagliaro 2002	Cisplatin, gemcitabine, ifosfamide	51		9.5	20/49 (41%)	2/49 (4%)	48/51 (94%) had a dose limiting hematologic toxicity				1
Lin 2007	Gemcitabine, ifosfamide	23	3.5	4.8	5/23 (22%)	1/23 (4%)		8/23 (35%)	5/23 (22%)	10/23 (43%)	
Pectasides 2001	Gemcitabine, ifosfamide	34	4	9	7/34 (21%)	1/34 (3%)	9/34 (27%)	4/34 (12%)	6/34 (18%)		0

Trial	Regimen	N	Progression-free survival (months)	Median overall survival (months)	Overall response rate	Complete response rate	Toxicity Grade 3-4				
							Neutropenia	Thrombocytopenia	Anaemia	Leucopenia	Toxic deaths
Dreicer 2003	Gemcitabine, Docetaxel	29		7.7	5/27 (17%)	1/27 (4%)		4/29 (14%)	8/29 (28%)		
Tsuruta 2011	Gemcitabine, Carboplatin, Docetaxel	26	5.0	12.6	9/16 (56%)	1/16 (6%)	28/35 (80%)	18/35 (51%)	15/35 (43%)		0

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Evidence tables

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
Witte 1998 **Topotecan**	N=44, confirmed incurable advanced urothelial carcinoma, ECOG PS <2, measurable lesion, one prior cytotoxic therapy and up to one biological response modifier regime, adequate organ function,	Median age 62 (36-83) 89% M/11% F	77% previous platinum-based chemo, 9% RT 5% local only disease, 14% local and systemic, 82% systemic only 36% soft tissue, 52% lymph node, 11% osseous, 36% lung, 32% liver 93% TCC, 5% adenocarcinoma	Topotecan 1.5mg/m^2 i.v. 30mins daily for 5 consecutive days, every 3 weeks for 6 cycles. If responding by end of 6 cycles, treatment could continue for 12 cycles. Doses modified for leukopenic fever, thrombocytopenic bleeding, and grade3-4 toxicity. Median 2 cycles (1-12). 7 dose reductions, 15 delays	Tumour response (ECOG criteria) Toxicity – NCI-CTC PFS Overall survival	
Beer (2008) Phase II **Iritonecan**	N=40, confirmed, measurable TCC of the urothelial tract stage T2-4, N0-3, M1 or unresectable stage T2-4, N+, and M0. Zubrod PS 0-2. Evidence of disease progression following one prior chemo regimen inc. Cisplatin or carboplatin	Median age 64.4 (46.4-81.5) 75% M / 25% F	25% PS 0, 60% PS 1, 10% PS2 73% visceral mets, 27% other (lymph, abodominal/pelvic wall, penis) 73% primary bladder 30% previous radiation	Iritonecan 350mg/m^2 (300mg in patients with previous RT to the pelvis) i.v. over 90mins, every 21 days. Starting dose of 50mg/m^2 allowed for patients over 65 years, PS 2, or increased bilirubin levels at discretion of physician. Standard antiemetics – dexamethasone 10mg i.v. and a 5-HT3 blocker were recommended. Median duration =2 months. 21 patients required at least 1 dose reduction.	Tumour response (RECIST) Overall survival PFS Toxicity	Treatment discontinued due to progression in 23 patients and toxicity in 6.
Wulfing 2009 **Lapatanib**	N=59, aged≥18 years, confirmed measurable locally advanced or metastatic TCC with progression after 1st-line platinum-based chemo. Karnofsky PS ≥70%, LVEF in normal limits, adequate organ function. Neo-/adjuvant prior therapy permitted.	Median age 64 (41-78) 71% M/ 29% F	22% PS 100, 27% PS 90, 36% PS 80, 15% PS 70 63% prior GC chemo, 10% prior MVAC chemo. 34% progressed within 3 months from prior therapy	Oral lapatinib 1250mg once daily. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. Dosage reduced to 1000mg/day when ≥grade 3 toxicity. All patients had a least 1 dose of lapatinib, median 8.14 weeks, range 0.40-55.10 weeks	Tumour response (RECIST) Toxicity – NCI-CTC PFS Overall survival	42% were non-assessable for response. 22 withdrew for progression, 13 SAEs, 1 withdrawal of consent
Gomez-Aubin 2007 **Bortezomib**	N=21, (17 with prior chemo for metastatic cancer) confirmed TCC with measurable metastatic disease, no more than 2 lines of chemo for metastatic disease (adjuvant and neoadjuvant allowed if >12mo before study), ECOG PS ≤1, adequate organ function.	Median age 70 (49-81) 70% M/ 30% F	50% PS 0, 50% PS 1 95% primary bladder 75% liver mets, 75% lung, 50% pelvis, 25% abdomen 40% prior adjuvant chemo, 55% systemic chemo	Bortezomib 1.3mg/m^2/day bolus i.v. on dyas 1,4,8,11, repeated every 21 days. Antiemetics not required. Median 3 cycles (1-3)	Tumour response (RECIST) PFS Overall survival Toxicity	Trial stopped early due to lack of treatment activity. 6-month survival = 34%
Rosenberg 2008 **Bortezomib**	N=24, confirmed urothelial TCC, one prior chemo for advanced or	Median age 64 (IQR, 57-72)	67% primary bladder, 38% renal pelvis, 29% ureter	Bortezomib at 1.3mg/m^2 i.v. days 1,4,8and 11 of a 21 day cycle. Given as	Tumour response (RECIST)	Study closed after interim analysis for

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
	metastatic disease, with progression during or after treatment. CTC PS 0-2 and ≤grade 1 neuropathy, RT or chemo completed >4 wks before trial. Adequate renal, liver function.	75% M/25% F	71% visceral metastases, 29% nodal mets only 54% prior Gem/Cis chemo, 25% prior Gem/Carbo	rapid bolus over 3-5s. Antiemtic premedications given at discretion of physician. Treatment continued if no disease progression and ≤grade 3 toxicity attributed to therapy lasting for 3 weeks. Up to two dose reductions were allowed. Median 2 cycles (1-12)	Toxicity (NCI-CTCAE) PFS Overall survival	lack of activity of therapy. One patient alive after 20 month f/up
Dreicer (2009) Phase II **Sorafenib**	N=22, confirmed TCC (pure or mixed) of the urothelium with progressive, regional or metastatic disease. ECOG PS 0-1. Progression after 1 chemo (metastatic setting). Adequate renal and hepatic function and marrow reserve.	Median age 66 (37-81) 64% M /36% F	36% ECOG PS 0, 64% PS1 68% primary bladder cancer 36% distant node mets, 46% liver mets, 41% bone mets, 64% lung mets Bajorin prognostic factors, 14% none, 86% 1 factor 77% prior surgery, 27% prior RT	Sorafenib: orally 400mg (2 tablets) twice daily for a total daily dose of 800mg. One cycle=56 days of therapy. No dose escalation was permitted. Modifications were allowed: dose level 2, 400mg/day; dose level 3, 400mg every other day. Modifications specified for myelosupression, and any grade 3-4 toxicity. Median cycles = 1 (1-4)	Tumour response (RECIST) Toxicity (NCI-CTC) 4-month PFS rate Overall survival	68% went off treatment due to progression, 18% due to toxicity. 4-months PFS =11%
Gomez-Aubin 2007 **Bortezomib**	N=21, (17 with prior chemo for metastatic cancer) confirmed TCC with measurable metastatic disease, no more than 2 lines of chemo for metastatic disease (adjuvant and neoadjuvant allowed if >12mo before study), ECOG PS ≤1, adequate organ function.	Median age 70 (49-81) 70% M/ 30% F	50% PS 0, 50% PS 1 95% primary bladder 75% liver mets, 75% lung, 50% pelvis, 25% abdomen 40% prior adjuvant chemo, 55% systemic chemo	Bortezomib 1.3mg/m^2/day bolus i.v. on dyas 1,4,8,11, repeated every 21 days. Antiemetics not required. Median 3 cycles (1-3)	Tumour response (RECIST) PFS Overall survival Toxicity	Trial stopped early due to lack of treatment activity. 6-month survival = 34%
Winquist 2005 **Oxaliplatin**	N=20, confirmed, measurable TCC, no more than 1 prior chemo regimen for metastatic disease. Patients may have additionally received adjuvant chemotherapy provided inthe interval between this and the first therapy for metastatic cancer was ≥6 months. ECOG PS 2 or less,	Median age 64 (45-81) 95% M/5% F	25% ECOG PS 0, 55% PS 1, 20% PS2, 45% prior chemo for metastatic disease, 35% prior adjuvant chemo 35% lung, 35% lymph node, 20% bladder/pelvis 55% platinum sensitive, 45% platinum resistant	Oxaliplatin 130mg/m^2 2-hour i.v. every 3 weeks. Antiemetic therapy with corticosteroids and a serotonin-receptor antagonist was required. Avoid cold drinks, water and air during treatment period. Discontinued if progression, illness or intolerable toxicity. Median 2 cycles (1-6).	Tumour response (WHO criteria) Toxicity	Trial stopped early due to lack of treatment activity. 2 patients discontinued due to pulmonary thromboembolism and 18 because of progression.
Galsky (2007) Phase II **Pemetrexed**	N=13, confirmed TCC of urothelial tract, One prior chemo regimen which included Cis, Carbo, Pac, Doc, or Gem. Neodjuvant or adjuvant or metastatic. Age>18years, PS >60%, adequate hematologic, hepatic, and renal function.	Median age 65 (57-82) Gender not reported	All patients received platinum-based therapy, 9/13 received carboplatin. Median PS 80 (70-90) 77% primary bladder, 77% prior chemo for metastatic disease. 100% had metastatic disease	Pemetrexed 500mg/m^2 i.v. over 10mins, every 21days. Dexamethasone 4mg orally twice daily on the day before, the day of, and the day after Pemetrexed. Folic acid 350-1000mg daily and vitamin B12 1000mcg every 9 weeks. Up to 9 cycles provided no evidence of progression or intolerable	Toxicity (NCI-CTC) Tumour response (RECIST)	8/13 stopped due to progression 3/13 due to toxicity. Study closed due to low response rates

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
				toxicity. Median 3 cycles (1-10)		
Sweeny 2006 **Pemetrexed**	N=47, confirmed stage IV urothelial TCC (pure/mixed) 1 prior chemo regime with progression any time after therapy for metastatic disease, or within 12 months of neo/ adjuvant setting. PS 0-1, adequate marrow, hepatic function & creatine clearance	Median age 64 (26-83) 81% M/ 19% F	98% TCC 60% PS 0, 34% PS 1, 4% PS2 16/39 platinum refractory 18 neo/adjuvant chemo, 29 metastatic chemo	Pemetrexed 500mg/m^2 as 10 min i.v. on day 1 of each 21 day cycle. Cycles repeated until progression or intolerable toxicity. 2 dose reductions allowed. GCSF only for grade 4 neutropenia, more than 3 days, neutropenic fever or infections in neutropenic patients.	Tumour response (SWOG criteria) Toxicity – NCI-CTC Overall survival PFS	Median f/up 9.2 months. 29 patients with prior metastatic therapy - 28% response rate, median survival 9.2 months.
McCaffrey (1997) **Docetaxel**	N=31 (30 assessable), confirmed advanced or metastatic TCC of the urothelial tract, relapsing or refractory to no more than 1 prior cisplatin-containing chemo. 4 weeks since prior chemo. Over 18yrs, PS ≥60%, adequate renal, and marrow function	Median age 61 (27-72) 83% M /17% F	Median PS 80 (70-90) 83% primary bladder, 17% renal pelvis. Median no. Of MVAC cycles 4 (2-8). Interval median 8 (1-64) months. 57% MVAC for metastatic disease, 43% adjuvant or neoadjuvant.	Docetaxcel: 100mg/m^2 over 1 hour i.v. every 21 days. Dexamethasone 20mg orally 12 and 6 hrs before therapy, followed by i.v. dexamethasone 20mg and diphenhydramine 50mg, 30mins before docetaxel. Median cycles 3 (1-11)	Toxicity (NCI-CTC) Tumour response	1 patient removed for recurrent mylosurpression, 2 patients deteriorated before 2nd cycle and failed to receive further therapy.
Choueiri 2012 **Docetaxel**	N=72 docetaxel+placebo, confirmed locally advanced or metastatic UC, progression of disease after platinum-containing chemotherapy. Age ≥18years, ECOG PS 0-1, No prior docetxel. Up to 3 prior therapies allowed (metastatic and/or within 2yrs of adjuvant or neoadjuvant). Adequate hematologic, renal and hepatic function.	46% aged ≥65 years 68% M/ 32% F	53% ECOG PS 1 64% visceral metastases, 38% liver metastases 39% >1 prior systemic therapy, 14% >2 prior systemic therapy 50% prior cystectomy, 21% prior RT, 11% prior paclitaxel, 69% bellmunt risk score >0	Docetaxel 75mg/m^2 1-hr infusion, day 1 and dexamethasone 8mg at 12, 3 and 1 hr before docetxel. Placebo for Vandetanib (1 tablet orally once daily). 21 day cycle. versus Docetaxel plus 100mg Vandetanib. Median f/up 7.1 months	Tumour response (RECIST) Toxicity – NCI-CTC PFS Overall survival	Double blind RCT of Docetaxel +Vandetanib vs. Docetaxel +placebo
Pronzato 1997 **Ifosfamide**	N=20, Metastatic or surgically unresectable TCC of the bladder, one line of prior systemic chemo, ≤75 years old, normal plasma bilirubin and creatinine, no cardiac disease,	Median age 68 (52-75) 80% M/ 20% F	Median PS 2 (1-2) Dominant tumour site: 15% lung, 25% lymph nodes, 30% bladder, 15% bone, 15% liver 50% prior MVAC, 15% CISCA, 30% Carbo/M/V	Ifosfamide 1000mg/m^2 2-hr infusion, 5 consecutive days, day 1-5. Mesna i.v. at 20% of ifosfamide dose, before treatment and orally at 40% after 4 &8 hrs from ifosfamide infusion. Treatment every 3 weeks provided bone marrow recovery occurred for 6 cycles.	Tumour response (WHO criteria) Toxicity	All patients died due to neoplastic disease progression.
Witte (1997) **Ifosfamide**	N=56, confirmed advanced TCC beyond surgical cure, PS <3, no more than one prior cytoxic therapy, no prior malignancies, adequate renal function.	Median age 67 (49-83) 77% M/23% F	71% PS 0-1, 29% PS2, 62% previous MVAC, 21% CMV, 11% other cisplatin combination, 6% other 32% soft tissue, 52% lymph node, 30% lung, 27% liver, 2% bone marrow	Ifosfamide i.v. over 4 hours at 3750mg/m^2 for 2 consecutive days every 3 weeks with mesna 2250mg/m^2 i.v. in three divided doses (every 4 hrs for 3 doses) starting just before ifosfamide daily for 2 days. Excessive renal and CNS toxicity was observed by	Tumour response (ECOG criteria) Toxicity (NCI-CTC) PFS Overall survival	No differences in PFS or OS between the 2 treatment schedules.

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
			84% primary bladder tumour, 14% renal pelvis 95% TCC, 3% adenocarcinoma, 2% squamous	the first 26 patients on this schedule. The remaining 30 patients recieved Ifosfamide i.v. 1500mg/m^2 daily for 5 days with mesna 750mg/m^2 i.v. in three divided doses (every 4 hrs for 3 doses) starting just before ifosfamide, for 5 days. All patients received the same total dose of ifosfamide (7.5g/m^2) during each course of therapy		
Gallagher 2010 **Sunitinib**	N=77, previously treated progressive metastatic urothelial carcinoma, one to four prior cytotoxic treatments in perioperative or metastatic setting. 4 weeks since end of prior treatment. PS ≥60, aged over 18 years, adequate organ function	Median age 64 (39-82) cohort A, 68 (45-84) cohort B 69% M/ 31% F	15% PS 60-70, 43% PS 80, 48% PS 90 64% primary bladder, 21% renal pelvis 82% visceral metastases, 18% lymph node only 61% metastatic setting, 39% perioperative	Sunitinib orally 50mg/day for 4 consecutive weeks, followed by 2 week rest – cohort A, or 37.5 mg continuously – cohort B Cohort B added as amendment after some recurrence of disease-related symptoms during 2-week break. Therapy continued until disease progression or unacceptable toxicity	PFS Overall survival Tumour response (RECIST) Toxicity – NCI-CTC	
Joly (2009) Phase II **Paclitaxel**	N=45, TCC of bladder or urothelial tract, progressive measurable disease after previous 1st line chemo for advanced disease (neoadjuvant, adjuvant or metastatic), life expectancy ≥3months, PS 0-2, normal hematology and serum bilirubin.	Mean age 64 (47-79) 80% M/20% F	82% PS 0-1, 18% PS2, 84% bladder primary, 96% TCC 7% locoregional relapse, 93% distant metastases 55% nodal mets, 52% pulmonary mets, 38% liver, 33% bone, 5% soft tissue, 87% previous surgery, 36% irradiation, 71% adjuvant chemo, 29% palliative chemo, 89% Gem/platinum regime	Paclitaxcel 80mg/m^2 i.v. over 1 hour days 1,8,&15 of a 28 day course, for a maximum of 6 cycles. Premedication with dexamethasone, dexchlopheniramine and ranitidine given i.v. before paclitaxel. Treatment stopped if persistent grade ¾ nonhematologic toxicity. Median 2 cycles (1-6)	Toxicity (NCI-CTC) Tumour response (RECIST) Quality of life (FACT-G, FACT bl, FACT-Taxane)	1-yr OS rate =22%. 62% stopped for progression, 13% for toxicity, 11% death. No decrease in QoL scores during chemo.17% improved QoL in at least 1 domain.
Papamichael (1997) **Paclitaxel**	N=14, advanced bladder or ureteric TCC. All patients received one treatment regimen before paclitaxel	Median age 68 (40-73) 64% M/36% F	21% ECOG PS 0, 50% PS1, 29% PS2 29% locally advanced, 79% metastatic disease	Paclitaxel 200mg/m^2 i.v. over 3 hours. Dexamethasone 20mg p.o. 12 and 6 hours before Pac, chlorpheniramine 10mg i.v. and cimetidine 300mg i.v. 30 min before treatment. Every 3 weeks.	Tumour response Toxicity	Short communication paper. Median f/up 54 days (1-240)
Vaughn 2002 **Paclitaxel**	N=31, 18 years or older, confirmed urothelial cancer, with progression regional or metastatic disease and one prior regimen of chemo. ECOG PS 0-2, adequate hematologic, renal and hepatic function. Life expectancy 3 months or longer,	Median age 66 (48-83) 84% M /16% F	87% ECOG PS 0-1, 13% PS2 87% TCC. 94% primary bladder cancer, 77% visceral (bone, liver or lung) metastases. 16% prior adjuvant chemotherapy, 39% MVAC for advanced disease, 13%	Paclitaxel 80mg/m^2 i.v. 1-hour, 4 weekly treatments. 20mg dexamethasone , 50mg diphenhydramine, cimetidine 300mg 30-60 mins before paclitaxel. Treatment until progression or intolerable toxicity. Median 3 cycles (1-8)	Toxicity – NCI-CTC Tumour response Overall survival	

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
			Pac/carbo, 42% RT			
Albers (2002) **Gemcitabine**	N=30, proven, measurable recurrent or progressing TCC, prior cisplatin-based chemo. No prior gemcitabine, chemo or RT within 4 weeks prior to study, no karnofsky PS <40, adequate liver and renal function.	Not reported	86% prior radical surgery with adjuvant MVAC/MVEC or CM, 7% cystectomy with neoadjuvant MEC, 7% primary MVEC/MVAC without radical surgery 43% regional lymph node and distant metastases	Gemcitabine 1250mg/m^2 on day 1 & 8 of a 21-day course i.v. 30 mins. Maximum 6 courses (18 weeks) 9/28 completed 6 courses of treatment, 15 did not receive maximum number due to progression, 4 dropped out due to toxicity or personal reasons	Tumour response (WHO criteria) Toxicity (WHO criteria) Quality of life (questionnaire from Spitzer et al) PFS Overall survival	
Lorusso (1998) **Gemcitabine**	N=35, inoperable or metastatic TCC of urinary tract who had previously received one platinum-containing chemo regimen	Median age 64 (38-74) 83% M/ 17% F	40% PS 0-1, 57% PS 2, 3% PS 3 83% previous radical cystectomy, 29% previous radiotherapy 83% received at least one previous cisplatin-based chemo for advanced disease (usually MVAC), 17% for adjuvant treatment, after removal of primary cancer, in absence of distant mets	Gemcitabine 1200mg/m^2 i.v. over 30 mins, days 1, 8 &15 of a 28 day cycle. 8mg odansetron 8mg i.v. prior to Gemcitabine. Maximum 8 cycles in responding patients or stable disease, discontinued if disease progression or severe toxicity. Mean 2.7 cycles	Tumour response (WHO criteria) Toxicity Overall survival PFS	
Akaza (2007) Phase II **Gemcitabine**	N=44, confirmed advanced or metastatic TCC of urothelium, with evidence of recurrence or progression following 1st line platinum chemo. ECOG PS 0-2, life expectancy of at least 3 months, age 20-74 years. No previously irradiated lesions	Median age 65 (35-74) 73% M / 27% F	68% PS 0, 27% PS 1, 5%, PS 2 2% Stage III, 21% Stage IV, 77% relapse after surgery 39% lung mets, 36% lymph node mets, 21% bone mets 46% primary bladder, 54% renal pelvis 80% previous MVAC, 9% MEC, 9% MVAC +other medication	Gemcitabine (monotherapy) 1000mg/m^2 i.v. 30mins, over 28 days (1 cycle), 3 consecutive weeks treatment (days 1, 8 and 15) followed by week of rest. Cycle repeated at least 3 times, or until disease progression or an intolerable adverse event. Dose reduction allowed (not lower than 800mg/m^2) if neutropenia, leucopoenia or thrombocytopenia. Median 3 cycles (1-21). 3 discontinued for safety reasons	Toxicity (WHO criteria) Tumour response Progression-free survival Overall survival	Open label study
Gebbia (1999) **Gemcitabine**	N=24, measurable urothelial carcinoma previously treated with chemotherapy and not more amenable with surgery, age ≤75 years, Karnofsky PS ≥60, life expectancy ≥3 months, adequate bone marrow function, at least 4 weeks since last treatment, no severe chemo-	Median age 61 (40-75) 79% M / 21% F	83% TCC, 62% previous surgery, 17% previous RT. 54% adjuvant chemo, 28% advanced disease chemo, 42% prior MVAC Sire of disease: 37% bone, 42% node, 37% liver, 33% lung, 33% pelvis 29% single site, 71% multiple	Gemcitabine (monotherapy) 1000mg/m^2/week i.v. diluted in 250cc of normal saline, 30mins once a week for 3 weeks followed by 1 week rest. Repeated every 28 days. Metoclopramide was employed as antiemetic therapy 15 mins before chemo, and as needed. If partial response or stable disease achieved,	Tumour response (WHO criteria) Overall survival Toxicity (WHO criteria)	

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
	related toxicities,		sites	chemotherapy was continued until progression or unacceptable toxicity. Chemo stopped at 6 months when complete regression. In cases of progressive disease, 3rd line chemo or best supportive care were given		
Halim 2013 Phase II **Methotrexate, Paclitaxel, epirubicin, carboplatin**	N=38, proven TCC treated with 1st line GC, PS 0-2, adequate bone marrow, platelet count, liver and renal function.	Median age 62 (range 46-69). 80% male, 20% female.	Metastatic sites: lymph nodes 40%, lung 35%. 75% ECOG PS 1, 25% PS2. Median time since prior chemo was 8 months (range 6-11)	Carboplatin (dose according to Calvert formula AUC 5) followed by i.v. Paclitaxel 175mg/m^2 for 1h on day 1. 30min before Paclitaxel, 20mg of dexamethasone with 4mg chlorpheniramine and 50mg ranitidine. Methotrexate 40mg/m^2 and epirubicin 40mg/m^2 both given as slow bolus on day 15. Repeated every 4 weeks. Continued until progression, severe toxicity, or up to 6 cycles.	Toxicity NCI-CTC Tumour response (WHO criteria) QoL assessed according to influence of therapy on PS, urological complaints, and pain.	2 patients with liver mets refused further treatment after 1st cycle.

5.2 Managing symptoms of locally advanced or metastatic bladder cancer

6.2.1 Bladder symptoms

Review question: What is the optimal pelvic radiotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

Rationale

Radiotherapy can be used to help patients with symptoms of incurable bladder cancer. It is most commonly used to treat bleeding from the bladder or pain from the bladder cancer itself or sites of spread. Radiotherapy is also used to improve local control rates in patients with advanced pelvic disease. Treatment is usually given between 1 and 10 fractions as an outpatient. Side-effects are related to the area treated but are usually well-tolerated. For example, bladder radiotherapy can result in short term urinary frequency and discomfort or diarrhoea and nausea. These symptoms can be easily managed using appropriate medication. There is little evidence of differences in toxicity and outcome of patients of different gender or age. The total dose and fractionation of radiotherapy varies across the UK. Some clinicians deliver palliative radiotherapy at the time of diagnosis whilst others delay treatment until the patient becomes symptomatic. There have been a limited number of randomised control trials in this topic.

This review should establish the optimum radiotherapy regime which benefits patients with incurable bladder cancer by establishing which doses and fractionation maximise symptom control and local disease control rates. The timing of radiotherapy (immediate at the time of diagnosis or delayed until patient is symptomatic) should also be evaluated.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with incurable locally advanced or metastatic bladder cancer	Palliative pelvic radiotherapy	Dose/fractionation, timing to treat, duration of treatment	• Overall survival • Progression free survival • Treatment-related mortality • Treatment related morbidity • Symptom control (haematuria/pelvic pain/urinary frequency) • Health-related quality of life, inc patient reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (DM)

Selection of studies

The information specialist (DM) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. Comparative studies and palliative radiotherapy series were selected for this review question.

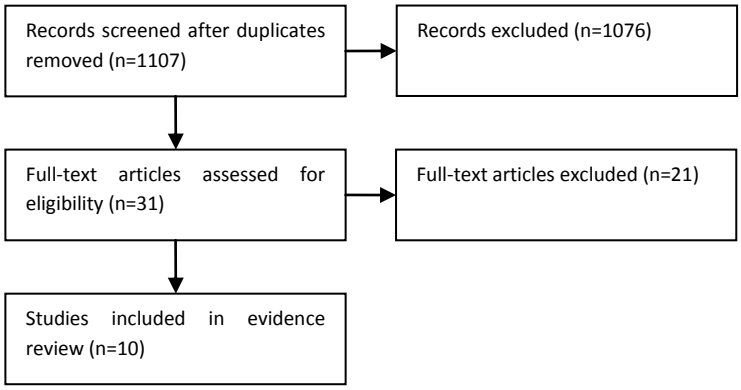
Data synthesis

Data was extracted into RevMan and risk ratios were calculated were possible. No meta-analysis was possible for this review question.

RESULTS

Result of the literature searches

Figure 75. Study flow diagram



Study quality and results

The included evidence is summarised in Tables 171-173.

Evidence statements

Moderate quality evidence about the relative effectiveness of two hypofractionated radiotherapy schedules (35 Gy in 10 fractions over two weeks versus 21 Gy in 3 fractions over one week) for local symptom control of muscle invasive bladder cancer came from one randomised trial (Duchesne *et al.*, 2000). 500 patients were randomised with three month follow-up data available in 272 patients. Overall symptom improvement, defined as improvement of at least one symptom by one grade without worsening another symptom, was 71% in those receiving 35-Gy compared with 64% in the 21-Gy arm, though there is uncertainty of a difference between treatments (absolute improvement 3%, 95% CI -6% to 12%). Comparing the 35 Gy group with the 21 Gy group for patients with specific pre-treatment symptoms, urinary frequency resolved in 43% and 42%, respectively, nocturia in 51% and 35%,

haematuria in 58% and 61%, and dysuria in 47% and 49%. Median survival was 7.5 months in both groups. Two-thirds of participants reported that quality of life symptom scores were either unchanged or improved by the end of treatment and at three months after treatment.

One observational study (Srinivasan *et al.*, 1994) provided low quality evidence about the relative effectiveness of hypofractionated (two-fraction) radiotherapy and conventional palliative radiotherapy in 41 patients selected by performance status. 59% of those receiving two-fraction radiotherapy had clearance of haematuria compared to 16% of those receiving conventional palliation (RR 3.74, 95% CI 1.25 to 11.19). Pain improved in 73% of those treated with two-fraction radiotherapy compared to 37% of those treated with conventional palliation (RR 1.97, 95% CI 1.04 to 3.75). All patients died during follow-up. Mean survival was 9.77 and 14.47 months in the hypofractionated and conventional radiotherapy groups respectively.

Very low quality evidence was reported from seven observational studies using various palliative radiotherapy regimens. Median survival ranged from six to nine months across studies. Complete palliation of symptoms was achieved in 51% of 65 elderly patients treated with 30 Gy in five fractions on a weekly basis, although 28 patients experienced transient worsening of their urinary symptoms with eight requiring hospital admission due to toxicities (McLaren *et al.*, 1997). Jose *et al.* (1999) reported a similar radiotherapy schedule with control of haematuria in 50%, frequency in 63%, dysuria 38%, and nocturia 5%. This study also reported toxicity rates of 36% for acute bowel and 63% for acute bladder toxicity. One study of short-term radiotherapy (7Gy 3 times or 5Gy 4 times) reported that none of the 17 patients with severe local symptoms improved after radiotherapy, although improvement was difficult to assess as 10 of these patients died within four months (Holmang *et al.*, 1995). Haematuria was present in 14 patients but it continued in only two after radiotherapy. Another study of short-term radiotherapy (Wijkstrom *et al.*, 1991) reported an improvement in tumour associated symptoms in 75/162 (46%) patients, although 42% had various minor acute side effects and over half the population were treated for tumours considered to be curable. Five-year survival in patients considered to be curable was 21%, compared to 6% in patients treated for bleeding and 0% for patients with other local symptoms.

Table 171. GRADE evidence profile: Palliative radiotherapy – 35Gy in 10 fractions versus 21Gy in 3 fractions

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**35 Gy-10**	**21 Gy-3**	**Relative (95% CI)**	**Absolute**	
Overall symptomatic improvement, Pre-treatment to end of treatment (improvement of at least one symptom by one grade without worsening of any other)											
1[1]	randomised trials	none	none	none	serious[2]	none	120/225 (53.3%)	115/232 (49.6%)	RR 1.08 (0.90 to 1.29)	3% (95% CI -6% to 12%)	⊕⊕⊕O MODERATE
Overall symptomatic improvement, Pre-treatment to 3-month assessment (improvement of at least one symptom by one grade without worsening of any other)											
1[1]	randomised trials	none	none	none	serious[2]	none	95/133 (71.4%)	89/139 (64%)	RR 1.12 (0.95 to 1.32)	7% (95% CI -2% to 13%)	⊕⊕⊕O MODERATE
Overall mortality											
1[1]	randomised trials	none	none	none	none	none	204/248 (82.3%)	198/252 (78.6%)	RR 1.05 (0.96 to 1.14)	Median survival 7.5 months in both arms	⊕⊕⊕⊕ HIGH
Progression-free survival											
0	No evidence					none	-	-	-	-	
Treatment-related mortality											
0	No evidence					none	-	-	-	-	
Quality of life (patient reported symptoms) (assessed with: Rotterdam Symptom Checklist)											
1[1]	randomised trials	none[3]	none	none	serious[2]	none	-	-	-	No difference in change of any symptom between arms[4]	⊕⊕⊕O MODERATE

[1] Duchesne (2000)

[2] Low number of events limits precision

[3] A high proportion of patients did not contribute information at the 3-month assessment due to death or deteriorating health. However, the reasons for missing data were similar between arms.

[4] Over 2/3 of patients contributing data noted no change or improvement in their QoL by the end of treatment and at 3 months. QoL symptoms were generally better at 3-months than post-treatment.

Table 172. GRADE evidence profile: Hypofractionated radiotherapy versus conventional palliative radiotherapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypofractionated RT	Conventional RT	Relative (95% CI)	Absolute	
Clearance of haematuria											
1[1]	observational studies	serious[2]	none	none	serious[3]	none	13/22 (59.1%)	3/19 (15.8%)	RR 3.74 (1.25 to 11.19)	433 more per 1000 (from 39 more to 1000 more)	⊕OOO VERY LOW
Clearance or improvement of haematuria (assessed with: Stopped completely or haematuria but without hospitalisation)											
1[1]	observational studies	serious[2]	none	none	serious[3]	none	19/22 (86.4%)	13/19 (68.4%)	RR 1.26 (0.89 to 1.79)	178 more per 1000 (from 75 fewer to 541 more)	⊕OOO VERY LOW
Relief or improvement in pain (assessed with: Opiates discontinued or at least a 50% reduction in opiate requirement)											
1[1]	observational studies	serious[4]	none	none	serious[3]	none	16/22 (72.7%)	7/19 (36.8%)	RR 1.97 (1.04 to 3.75)	357 more per 1000 (from 15 more to 1000 more)	⊕OOO VERY LOW
Overall mortality rate											
1[1]	observational studies	serious[2]	none	none	serious[3]	none	22/22 (100%)	19/19 (100%)	-	Mean OS 9.77 versus 14.47 months in favour of conventional RT	⊕OOO VERY LOW
Progression-free survival											
0	No evidence										
Treatment-related mortality											
0	No evidence										
Treatment-related morbidity											
0	No evidence										
Quality of life											
0	No evidence										

[1] Srinivasan (1994); [2] Patients selected for treatments based on performance status. Hypofractionated group were older and with poor performance status (WHO grade 4 or more)
[3] Low number of events/small sample size limits precision; [4] No pain data for 7 (17%) patients

Table 173. GRADE evidence profile: Palliative radiotherapy for bladder cancer (observational studies)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Palliative radiotherapy	Control	Relative (95% CI)	Absolute	
Symptom control (complete relief or improvement of symptoms e.g. haematuria, frequency)											
7[1]	observational studies	serious[2]	none	none	serious[3]	none	43%-51% across studies (see Table 1)	-	-	-	⊕OOO VERY LOW
Overall survival											
7[4]	observational studies	serious[2]	none	none	serious[3]	none	Median OS 6 to 9 months across studies	-	-	-	⊕OOO VERY LOW
Progression-free survival											
2[5]	observational studies	none	none	none	serious[3]	none	Median PFS 8.3 months to 14 months	-	-	-	⊕OOO VERY LOW
Treatment-related mortality											
1[6]	observational studies	none	none	none	serious[3]	none	5/96 (5.2%)	-	-	-	⊕OOO VERY LOW
Treatment-related morbidity (acute urinary or GI toxicity)											
7[1]	observational studies	serious[2]	none	none	serious[3]	none	Around 1/3 to 2/3 of patients reported acute toxicity across studies (see Table 1)	-	-	-	⊕OOO VERY LOW
Quality of life											
0	No evidence available										

[1] Jose (1999); McLaren (1997); Holmang (1996); Salminen (1992); Wijkstrom (1991); Spagnoletti (2010); Kouloulias (2013)

[2] In Jose (1999) outcomes not reported separately for patients treated for local control and those treated for palliation. For all studies - outcome data not available for all patients due to poor health and high mortality rates. Length of follow-up not reported.

[3] Small sample size and low number of events in each study limits precision,

[4] Jose (1999); McLaren (1997); Holmang (1996); Salminen (1992); Wijkstrom (1991); Spagnoletti (2010); Saunders (2006)

[5] Salminen (2002); Kouloulias (2013)

[6] Holmang (1996)

References to included studies

Duchesne, GM et al. A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. International Journal of Radiation Oncology, Biology, Physics 2000; 47(2): 379-388.

Holmang, S and Borghede, G. Early complications and survival following short-term palliative radiotherapy in invasive bladder carcinoma. Journal of Urology 1996; 155(1): 100-102.

Jose, CC et al. Hypofractionated radiotherapy for patients with carcinoma of the bladder. Clinical Oncology (Royal College of Radiologists) 1999; 11(5): 330-333.

Kouloulias, V et al. Evaluation of Acute Toxicity and Symptoms Palliation in a Hypofractionated Weekly Schedule of External Radiotherapy for Elderly Patients with Muscular Invasive Bladder Cancer. International Braz J Urol 2013; 39(1): 77-82

McLaren, DB, Morrey, D, and Mason, MD. Hypofractionated radiotherapy for muscle invasive bladder cancer in the elderly. Radiotherapy and Oncology 1997; 43(2): 171-174.

Salminen, E. Unconventional fractionation for palliative radiotherapy of urinary bladder cancer. A retrospective review of 94 patients. Acta Oncologica 1992; 31(4): 449-454.

Saunders, D and Kiltie, A. Palliative radiotherapy for bladder cancer: The Leeds teaching hospitals experience. Radiotherapy and Oncology 2006; 81: S532-S532.

Spagnoletti, G et al. Palliative radiotherapy for bladder cancer: A small retrospective study. Anticancer Research 2010; 30(4): 1515

Srinivasan, V, Brown, CH, and Turner, AG. A comparison of two radiotherapy regimens for the treatment of symptoms from advanced bladder cancer. Clinical Oncology (Royal College of Radiologists) 1994; 6(1): 11-13.

Wijkstrom, H et al. Short-term radiotherapy as palliative treatment in patients with transitional cell bladder cancer. British Journal of Urology 1991; 67(1): 74-78.

References to excluded studies (with reasons for exclusion)

Cameron, MG et al. Patient reported outcomes of symptoms and quality of life among cancer patients treated with palliative pelvic radiation: a pilot study. BMC Research Notes 2011; 4: 252

Reason: pilot study (n=22), mostly prostate cancer, outcomes not relevant to PICO

Caravatta, L et al. Short-course accelerated radiotherapy in palliative treatment of advanced pelvic malignancies: a phase I study. International Journal of Radiation Oncology, Biology, Physics 2012; 83(5): e627-e631.

Reason: mostly gynaecologic cancers, phase I study (n=27)

Yamaguchi, S et al. Palliative radiotherapy in patients with a poor performance status: The palliative effect is correlated with prolongation of the survival time. Radiation Oncology 2013; 8(1)

Reason: not pelvic RT, mostly lung cancer patients

Van, WN et al. Determination of margins for pelvic lymph nodes for the treatment of bladder cancer. International Journal of Radiation Oncology Biology Physics 2011; 81(2 SUPPL. 1): S449-S450.

Reason: outcomes not relevant to PICO

Toscano, G et al. Role of radical radiotherapy (RRT) in the treatment of inoperable invasive bladder cancer in the elderly. European Journal of Cancer 1997; 33: 140-140.

Reason: unclear if relevant to PICO, abstract only

Ok, J-H, Meyers, FJ, and Evans, CP. Medical and surgical palliative care of patients with urological malignancies. Journal of Urology 2005; 174(4 I): 1177-1182.

Reason: Expert review

Nishioka, K et al. Organ-conserving definitive radiotherapy for locally advanced bladder carcinomawith image-guided local boost. International Journal of Radiation Oncology Biology Physics 2011; 81(2 SUPPL. 1): S449

Reason: abstract only, insufficient information to include

Moonen, L et al. A feasibility study of accelerated fractionation in radiotherapy of carcinoma of the urinary bladder. International Journal of Radiation Oncology, Biology, Physics 1997; 37(3): 537-542.

Reason: population not relevant to PICO (radical radiotherapy)

Lutz, ST et al. A review of hypofractionated palliative radiotherapy. Cancer 2007; 109(8): 1462-1470.

Reason: expert review

Hoskin, PJ. Optimisation of palliative radiotherapy. European Journal of Cancer, Supplement 2007; 5(5): 380-382.

Reason: expert review

Harris, V, Warren-Oseni, K, and Huddart, R. Radiotherapy planning study comparing VMAT, IMRT and 3D-CRT in the treatment of bladder and pelvic lymph nodes. Radiotherapy and Oncology 2012; 103: S589-S590.

Reason: abstract only, unclear if relevant to PICO

Fetscher, S, Schmielau, J, and Schulze-Seemann, W. Five-year, disease-free survival after repeat palliative multimodality therapy in a patient with recurrent metastastic bladder cancer. The scientific world journal 2007; 7: 1736-1742.

Reason: case study

De, SM et al. Combined chemo-radiotherapy with gemcitabine in patients with locally advanced inoperable transitional cell carcinoma (TCC) of the urinary bladder and/or in patients ineligible for surgery: Results of a phase I trial. Annals of Oncology 2010; 21: viii274

Reason: not relevant to PICO (chemo-radiotherapy)

Carillio, G et al. A phase I trial of conformal radiotherapy plus gemcitabine for the treatment of locally advanced or relapsed bladder cancer. Annals of Oncology 2006; 17: XI77-XI77.

Reason: not relevant to PICO (chemo-radiotherapy)

Graham, JD et al. Palliative radiotherapy for muscle invasive bladder cancer: Final results of a prospective randomised trial of two radiotherapy schedules. British Journal of Cancer 2000; 83: 27-27.

Reason: duplicate of Duchesne, abstract only

vom Dorp, F, Borgermann, C, and Rubben, H. Palliative therapy concepts for patients with urothelial cancer of the urinary bladder. Urologe 2007; 46(1): 54-55.

Reason: foreign language

Fossa, SD. Pelvic Palliation Radiotherapy of Advanced Bladder-Cancer. International Journal of Radiation Oncology Biology Physics 1991; 20(6): 1379-1379.

Reason: editorial

Wesson, MF. Radiation-Therapy in Regionally Advanced Bladder-Cancer. Urologic Clinics of North America 1992; 19(4): 725-734.

Reason: expert review on curative radiotherapy

Spanos, J et al. Phase II study of multiple daily fractionations in the palliation of advanced pelvic malignancies: Preliminary report of RTOG 8502. International Journal of Radiation Oncology Biology Physics 1989; 17(3): 659-661.

Reason: mostly gynaecologic and colorectal malignancies, results not reported separately

Vitale, V. When to implement radiotherapy. Tumori 2003; S113-S113.

Reason: foreign language, abstract only

Zygogianni, A et al. A weekly hypofractionated radiotherapeutic schedule for bladder carcinoma in elderly patients: local response, acute and late toxicity, dosimetric parameters and pain relief. Journal of B.U.On. 2013; 18(2): 407-412.

Reason: appears to be same study as Kouloulias (2013)

Evidence tables

<table>
<tr><th>Study, country</th><th>Study type, study period</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Duchesne 2000

UK</td>
<td>Randomised trial

1992-1997</td>
<td>500 patients (460 included in symptom improvement analysis) MIBC causing local symptoms, life expectancy at least 3 months, no chemo. Either unfit for radical treatment because of age or general medical condition, or tumour stage too advanced for radical treatment (T4b,N+,M1).</td>
<td>
<table>
<tr><th></th><th>35 Gy-10 N (%)</th><th>21 Gy-3 N (%)</th></tr>
<tr><td>Median age</td><td>79</td><td>80</td></tr>
<tr><td>Male</td><td>182 (73)</td><td>181 (72)</td></tr>
<tr><td>Female</td><td>66 (27)</td><td>71 (28)</td></tr>
<tr><td>PS 0</td><td>28 (11)</td><td>32 (13)</td></tr>
<tr><td>PS 1</td><td>116 (47)</td><td>122 (49)</td></tr>
<tr><td>PS 2</td><td>83 (34)</td><td>82 (33)</td></tr>
<tr><td>PS 3</td><td>19 (8)</td><td>14 (5)</td></tr>
<tr><td>Unfit for Rx</td><td>164 (66)</td><td>157 (62)</td></tr>
<tr><td>Too advanced</td><td>84 (34)</td><td>95 (38)</td></tr>
<tr><td>TCC</td><td>228 (93)</td><td>226 (90)</td></tr>
<tr><td>G1</td><td>3 (1)</td><td>5 (2)</td></tr>
<tr><td>G2</td><td>47 (19)</td><td>41 (16)</td></tr>
<tr><td>G3</td><td>190 (77)</td><td>195 (78)</td></tr>
<tr><td>Gx</td><td>6 (3)</td><td>10 (4)</td></tr>
<tr><td>N0</td><td>85 (34)</td><td>71 (28)</td></tr>
<tr><td>N+</td><td>29 (12)</td><td>53 (21)</td></tr>
<tr><td>Nx</td><td>133 (54)</td><td>128 (51)</td></tr>
<tr><td>M0</td><td>132 (54)</td><td>137 (54)</td></tr>
<tr><td>M1</td><td>13 (5)</td><td>27 (11)</td></tr>
<tr><td>Mx</td><td>102 (41)</td><td>88 (35)</td></tr>
<tr><td>Hem g/dl</td><td></td><td></td></tr>
<tr><td><10</td><td>36 (15)</td><td>30 (13)</td></tr>
<tr><td>≥10</td><td>203 (85)</td><td>210 (87)</td></tr>
<tr><td>SCr</td><td></td><td></td></tr>
<tr><td>Normal</td><td>121 (52)</td><td>115 (49)</td></tr>
<tr><td>elevated</td><td>111 (48)</td><td>121 (51)</td></tr>
</table>
</td>
<td>21 Gy in 3 fractions on alternate weekdays over 1 week

RT planning and treatment at discretion of clinician although advised that megavoltage irradiation used and treatment volume should encompass the bladder and tumour and not whole pelvis. 2, 3, or 4 field techniques were permissible, preferably treating all fields for each fraction.</td>
<td>35 Gy in 10 fractions over 2 weeks</td>
<td>3-month assessment for symptomatic assessment. Median follow-up for OS not reported.</td>
<td>Symptom improvement: 120/225 (53%) 35-Gy and 115/232 (50%) 210Gy had noted overall bladder and bowel symptomatic improvement by end-of-treatment assessment. Absolute difference 3% (-6% to 12%).
No evidence of a difference between treatments for changes of symptoms from pre-treatment to 3-month assessment.
Haematuria alleviated in 88%, frequency in 82%, dysuria in 72% and nocturia in 64%.
95/133 (71%) 35-Gy and 89/139 (64%) 21-Gy achieved overall symptomatic improvement from pre-treatment to 3-month assessment Absolute difference 7% (-2% to 13%).
Quality of life (Rotterdam Symptom</td>
<td>MRC</td>
<td>Adequate randomisation, groups comparable at baseline, power calculations conducted, similar drop-out rate in both groups. Reasons for lack of data at 3-month assessment similar in both groups.</td>
</tr>
</table>

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							Checklist): Most patients reported no overall change or an improvement. No difference in change of any symptom between 2 treatment arms. **Overall survival:** 402 (204/248 35Gy, 198/252 21-Gy) patients died (HR 0.99, 0.82-1.21). 3-mo survival 77% in both arms. Median survival=7.5mo		
Srinivasan (1994) UK	Observational study (appears retrospective) 1982-1989	41 patients T3-4, Grade 2-3 TCC treated by palliative radiotherapy	19 patients with reasonable PS (WHO grade ≤3) treated with conventional palliative treatment; 22 patients with poor performance status (WHO grade ≥4) accelerated radiotherapy. Mean age 78.4 years in 2-fraction group compared to 71.6 y in conventional group.	Conventional palliative treatment 4500cGy in 12 fractions over 26 days Both used supervoltage photons. From 1984 volume was localised with CT.	Accelerated radiotherapy 1700cGy in 2 fractions over 3 days.	Not reported	**Clearance of haematuria:** 59% (13/22) 2-fraction, 16% (3/19) conventional **Improvement of pain:** 73% (16/22) 2-fraction, 37% (7/19) conventional RT. Disease was fatal in all patients **Overall survival:** Mean 9.77 months 2-fraction vs 14.47 months conventional		No pain data for 7 patients.
Jose (1999) UK	Observational study (appears prospective) 1988-1992	65 patients over 70yrs with MIBC who were not suitable for standard radical radiotherapy regimen of 64Gy in 32 fractions over 6.5wks.	<table><tr><td></td><td></td></tr><tr><td>Median age</td><td>81</td></tr><tr><td>Age range</td><td>71-95</td></tr><tr><td>Male</td><td>38</td></tr><tr><td>Female</td><td>27</td></tr><tr><td>TCC</td><td>63</td></tr><tr><td>Squamous cell</td><td>2</td></tr><tr><td>G2</td><td>20</td></tr><tr><td>G3</td><td>42</td></tr></table>	Weekly 6Gy, total dose 30-36 Gy in 5/6 fractions when treatment intent was local control of disease. Treatment terminated at 12-24 Gy in 10 pts when aim was palliation.	N/a	Median 29 months (range 20-70)	**Overall survival:** Median survival 35 weeks, 2-yr survival 21%. 37 (62%) achieved complete response (6 of these relapsed locally and 1 both locally and with mets). **Symptom control:**		Outcomes not reported separately for patients treated for local control and those treated for palliation.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
			Gx: 3 Dose (Gy) 36: 30 30: 25 24: 5 18: 3 12: 2 54 patients had T3 or T4 disease, 6 had distant mets.				Haematuria controlled in 7/14 (50%) and frequency in 10/16 (63%), dysuria 3/10 (38%), nocturia 1/27 (5%) **Toxicity:** 23 (36%) acute bowel toxicity, 40 (63%) acute bladder toxicity. 1 urinary obstruction (RTOG grade 4). 7/16 (44%) late bladder morbidity, 1 (6%) late rectal morbidity.		
McLaren (1997) UK	Retrospective review Study period not reported	55 patients unsuitable for radical treatment due to poor performance status, comorbid illness, or tumour stage.	Median age: 78 Male: 45 Female: 20 WHO PS 0: 0 WHO PS1: 18 WHO PS 2: 34 WHO PS 3: 13 WHO PS 4: 0 T2: 34 T3: 24 T4a: 7 N0: 63 N1: 2 M0: 61 M1: 4 G1: 0 G2: 29 G3: 36	Patients treated supine using a ct planned volume. The empty bladder and perivesicular tissues incorporated with a 1.5cm margin, typical treatment volume 1000cm^3. 10MV linear accelerator using open anterior and 2 wedged postero-oblique fields. Hyperfractionated schedule. Once weekly 6Gy fractions to 100% isodene as target minimum to 30Gy and 36Gy	N/a	Median follow-up for those still alive was 18mo (range 5-41)	**Palliation from symptoms:** At 1-mo post-RT review 28/55 (51%) were completely palliated from symptoms. 7 (13%) noticed improvement in urinary symptoms. In total 73% were asymptomatic or experienced an improvement in symptom control 1 month from RT. 17 (26%) failed to benefit from treatment – 10 worsening urinary symptoms, 7 persistent bowel symptoms. **Toxicity:** 28 (43%) worsening of symptoms – 12 urinary toxicity, 9 bowel toxicity, 7 bowel		

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							and urinary toxicity. 8 (125) required inpatient admission for toxicity, **Survival:** 52 deaths, median survival 9mo, range 0-41.		
Holmang (1996) Sweden	Retrospective cohort study 1981-1992	96 patients unfit for cystectomy, full-dose RT, or CT treated with short course pelvic RT.	T2M0: 13 T3M0: 36 T4M0: 26 T2-T4 M+: 21 Median age: 80 (51-90) Ureteral obstruction: 14 unilateral, 24 bilateral haematuria: 14 Severe local symptoms: 17	RT generated by 8MV, 11 MV, 16 MV linear accelerator, 2-field technique. 15 patients treated with 5 Gy, 4 times to max 20Gy, 81 treated with 7 Gy, 3 times total 21 Gy. Treatment every 2 days.	n/a		**Median survival:** 6 months. 4 alive with no evidence of disease min 44 mo (T2-T3M0). **Early side effects** 25 severe GI/bladder 22 of these hospitalised for median 10 days. Side effects in 20 other patients who were already under care at hospital or nursing home. **Treatment-related mortality:** n=5 **Symptom relief:** 17 had severe local symptoms before treatment. No patients improved after RT. (however 10/17 died with 4 mo and 2 treated with ureteral catheters).		
Salminen 1992 Australia	Retrospective review 1983-1985	94 locally advanced, recurrent or metastatic BCa treated with external RT for palliation of local disease. Excluded prior	Median age: 79y (55-92) Male: 69 (73%) Female: 25 (27%) Haematuria: 85% N+: 15 (16%) M+: 15 (16%) Nx: 42 T2: 33 (35%) T3: 24 (26%)	Megavoltage beams from 4 or 6 MeV linear accelerator. Total mid point dose 30Gy in 6 fractions, 2 fractions/week at least 2 days apart over 3 weeks. 86% treated with 2	n/a		**Symptom relief:** 40 (43%) complete relief, 29% partially resolved symptoms. 8/17 patients with catheter prior to RT did not need it after RT. **Survival:** Median survival 9.6 months. 29%		

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
		pelvic RT.	T4: 30 (32%) Hydronephrosis: Unilateral 27 Bilateral 6 Indwelling catheter before RT: 17 (18%)	opposed anterior and posterior fields. 11 patients with 3 fields and 2 with 4 fields.			survived at 2 years and 13% at 5 years Median DSS 13.3 mo Median time to progression 8.3 mo **Toxicity:** 15 (16%) grade 3 diarrhoea requiring treatment. 15 (16%) nausea/vomiting, 19 (20%) frequency or incontinence. Late effects >3mo after RT in 27 (29%). Including urethral stricture, proctitis, cystitis, haematuria.		
Spagnoletti (2010) Italy	Retrospective observational study 2006-2009	25 with T2-T4, N0-2 bladder cancer receiving palliative external radiotherapy	21 males, 4 females presented with haematuria and local pain and their medical condition or disease status prevented an operation or radical therapy. Mean age 77 (range 63-87)	Different fractionation schedules were used: conventional irradiation 20-30 fractions up to 40-54GY in 16 cases and hypofractionated RT with 1-3 fractions of 6-10 Gy once a week in 9 cases. Treatment with 3 or 4 10-18 MV photon beams.	n/a		**Symptom relief:** Haematuria improved 13/17 patients (76.5%). Pain and /or dysuria improved decreased in 5/12 (41.7%). Mean duration of response 17 weeks (3-118). Complete haematuria clearing 2/9 (22%) with conventional fractionation and 4/8 (50%) in hypofractionated group. 6Gy were least useful treatments, up to 3 fractions only a slight benefit observed. **Toxicity:** No significant difference in toxicity between two schedules.		Abstract only

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
							12 (47%) acute genitourinary toxicity. No significant late toxicity **Overall survival:** 24% at 1-year and 12% at 2 yrs. Mean survival 32 weeks (range 4-120)		
Saunders 2006 UK	Retrospective review	43 bladder cancer patients receiving palliative radiotherapy	9 Node positive, 9 T4 disease, 12 had a performance status of 3. Median age 85 (range 70-92).	All treated using anterior-posterior parallel-opposed fields with a mid plane dose of 20Gy in 5 fractions (n=36) or 8 Gy single fraction (n=7). 16 had RT planned using a standard 2D simulator based on bony landmarks. 27 patients were planned using 3D virtual simulation with fields encompassing the bladder with a margin of 1.5-2cm	2D versus 3D virtual simulation planning	Not reported	**Overall survival:** Median OS =6 months for male and 13 months for male (sic) patients. 12 month OS 31%. Use of virtual simulation did not alter survival but did demonstrate a trend towards decreased treatment volumes for female patients and increased treatment volumes for male patients.		Abstract only
Wijkstrom 1991 Sweden	Observational study 1974-1986	162 patients not fit enough for radical treatment who received palliative radiotherapy	Mean age: 78 (range 54-96) Men: 94 Female: 68 Primary tumour: 103 Recurrent: 59 T1: 19 T2: 32 T3: 73 T4: 34	Short term radiotherapy (7Gy 3 times a day over 5 days) total dose 21 Gy. 8MeV photons were used from anterior and posterior opposing fields with a 12x15cm field size.	N/a	Not reported	**Survival:** Patients who responded to RT had a relative 5-yr survival of 58% compared to 4% in those who failed to respond. No difference in survival for age, gender, grade or primary/recurrent tumour.		Endoscopic check impossible in 57 (35%) patients. Data on side effects lacking in 64 patients

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
				In 8 patients RT was repeated 6-12mo later and 1 patient received 3 courses of 21 Gy No consistent screening for metastases was attempted Indications for RT was cure in 85 patients (advanced age or ill health), bleeding in 52 and local symptoms in 25.			For patients considered to be curable 5-yr survival was 21% compared with 6% for bleeding and 0% for other symptoms. **Palliation:** improvement in tumour-associated symptoms noted in 75 patients. 27 showed improvement in bleeding, Severe local symptoms improved or disappeared in 14/25 patients. Results hard to assess due to insufficient information. **Complications**: 68/162 (42%) suffered acute side effects but usually minor. Late serious complications in 5 (3%) patients.		
Kouloulias 2013 Greece	Prospective observational study 2005-2011	58 patients with organ-confined (cT1-2, N0) bladder cancer. All inoperable, with poor PS, >75yrs. Excluded previous pelvic RT or cystectomy, LN mets, distant mets or hip prosthesis.	Median age: 77 (70-91) T1: 12 T2: 46 PS 60-70%: 10 PS 50-60%: 48 Male/female: 47/11	Hypofractionated 3DCRT- virtual CT planning used. Clinical target volume (the bladder) and planning target volume obtained by expanding CTV with a margin of 1cm in each direction and of 0.5cm posteriorly. Entire bladder was treated using 4-field technique with 15	N/a	3 months after RT treatment	**Acute Grade 1-2 GI toxicity:** 13/58 (22%) **Acute Grade 1-2 GU toxicity:** 19/58 (33%) No grade 3 or higher GI or GU toxicity. **Patient-reported pain:** VAS score improved from 4.2 (±1.1) to 1.8 (±0.6) ($p<0.001$). **Palliation of haematuria:** 55/58 (94.8%). **Progression-free survival:** Median 14		Also in evidence review for topic L2. Data very unclear. Unsure if rates refer to patients with or without symptom palliation before and after treatment.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
				MV x-ray energy beams. 36Gy in 6 weekly fractions.			months		

5.2.2 Loin pain and symptoms of renal failure

Review question: What is the best way to manage cancer related ureteric obstruction in patients with bladder cancer?

Rationale

In patients with locally advanced bladder cancer, with or without metastases, the tumour can sometimes obstruct one or both ureters (the tubes connecting the kidneys to the bladder). If only one kidney is obstructed, the opposite kidney can usually maintain normal kidney function. Here the decision to intervene is often based on whether the patient has symptoms such as loin pain or whether optimal kidney function is essential e.g to enable safe administration of systemic chemotherapy. However, if both kidneys are obstructed then urine cannot pass and the patient will develop kidney failure which if untreated is fatal. Fortunately this type of presentation is relatively uncommon. Historically these patients were often managed conservatively with no intervention and this is still one option. However the obstruction can be relieved either by inserting a stent (an internal plastic drainage tube) under general anaesthetic or by a radiologist inserting a nephrostomy (a plastic drainage tube which comes out through the skin and drains into an external bag).

There are no current guidelines or good quality randomised trials in this area and treatment is often based on opinion or local resources leading to widespread variations in practice across the UK.

Not treating the obstruction is uniformly fatal and in the last decade, as a result of a greater public awareness of issues surrounding end of life care, is often unacceptable to patients and their carers. The benefit of surgical insertion of a stent is that the patient does not have an external urine bag. It may also be possible to remove some of the obstructing tumour. However, the tumour is often very advanced making it impossible to identify the ureteric openings to insert the stent and the patient who is often very sick from kidney failure will have been exposed to the risks of an anaesthetic but with an unsuccessful outcome. Even with successful stenting the obstructing tumour can prevent adequate urine drainage necessitating subsequent nephrostomy drainage.

The benefit of a nephrostomy insertion is that the procedure can be carried out under light sedation, if necessary in a ward setting (e.g ITU) and improvement in kidney function is independent of the tumour obstruction further down the ureter. The main disadvantage is that if the patient's blood clotting is deranged as is often the case in kidney failure, then nephrostomy insertion is potentially dangerous due to the risks of causing internal bleeding. It also requires an experienced interventional radiologist which may not be available particularly out of hours or in a small DGH.

The benefits and harms of doing nothing or intervention with either a stent or a nephrostomy should be outlined. Recommendations should also cover whether the obstruction affects one or both kidneys and, in the latter group, whether or not the patient has reached end of life care.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with cancer related ureteric obstruction	Urinary stent Surgery - urinary diversion Percutaneous nephrostomy	Best supportive care Each other	• Improvement of renal function • Symptom relief • Treatment related morbidity • subsequent chemotherapy • Subsequent cystectomy • Health-related quality of life inc patient reported outcomes • Overall survival

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria. Studies were also considered if they included patients with ureteric obstruction caused by malignancies other than primary bladder cancer. Studies must include at least 50 patients with malignant obstruction to be included.

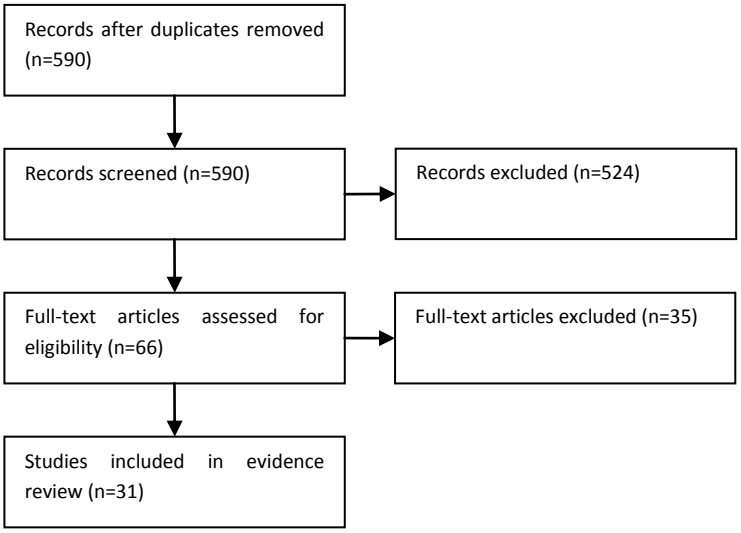
Data synthesis

Data was extracted into GRADE. No meta-analysis was possible for this review question. A narrative summary of the evidence is presented.

RESULTS

Result of the literature searches

Figure 76. Study flow diagram



Study quality and results

30 retrospective case series studies and one prospective quality of life study were identified for this evidence review. Evidence is summarised in Tables 174-182.

Narrative summary of the evidence

Open nephrostomy and ureteral stents

Very low quality evidence was provided by one retrospective review of open surgical techniques and non operative urinary diversion for malignant ureteral obstructions (Zadra, 1987). After 1981, no patients required open nephrostomy.

Improvement of renal function

60/88 patients undergoing bilateral procedures had normal renal function after diversion, although this outcome was not reported separately for each procedure.

Treatment-related morbidity

The overall complication rate was highest for open nephrostomy (57%, including dislodgement and infection/sepsis). Complication rates for percutaneous nephrostomy (PCN) and retrograde stents were 25% (dislodgement, blockage, infection) and 19% (dislodgement, blockage), respectively. Prostate and bladder tumours were the most difficult to divert by retrograde stents because the ureteral orifices were more difficult to see or were invaded by the tumour.

Overall survival

The average survival of patients undergoing open nephrostomy was 3.8 months. In the 38 patients who died after retrograde stenting or PCN, the average overall survival was 6.5 months.

No evidence was available about the impact of open nephrostomy and ureteral stents on subsequent chemotherapy, subsequent cystectomy, symptom relief or health related quality of life

Retrograde stents

Five retrospective series provided evidence about retrograde stents for malignant obstructions. Evidence for all outcomes was of very low quality. In Shekarriz (1999) patients underwent PCN or retrograde stenting, but it is not clear how many participants had each procedure and the outcomes were not reported separately per procedure.

Improvement of renal function

Three studies (313 patients) reported that average serum creatinine levels decreased after retrograde stent placement by 34% to 57% across studies (Shekarriz 1999; Ganatra 2005; Kamiyama 2011).

Symptom relief

One study reported that 50/90 (56%) participants showed resolution of hydronephrosis and flank pain or renal failure after stent placement (Chung 2004).

Treatment-related morbidity

A 65.6% complication rate was reported by three studies (302 participants), including catheter complications, hematuria and UTI (Shekarriz 1999; Ganatra 2005; Kamiyama 2011). Izumi (2011) did not report treatment-related morbidity but reported that there were no major complications with retrograde stent placement.

Overall survival

Four studies (374 participants) reported an average length of overall survival, ranging from 2.2 months to 11.1 months. Izumi (2011) reported a median survival time of 7.6 months, with Scr before stent placement of 1.2 mg/dl or greater, no treatment after stenting, and cancer group (especially non-gynaecologic cancers) were prognostic factors for unfavourable overall survival. Gastrointestinal (GI) cancer was associated with a shorter overall survival. 57% of the population in Kamiyama (2011) had primary GI cancer, and this study had the shortest median survival of 2.2 months (range 1-546 days). Type of cancer did not predict stent failure in one study, although 56% of participants with invasion into the bladder on cystoscopy progressed to PCN referral (Ganatra 2005).

Subsequent chemotherapy

26/61 (42.6%) of patients received chemotherapy after treatment of malignant obstruction (Izumi 2011). In total 39/61 (64%) received some form of treatment for cancer after stent placement.

Percutaneous nephrostomy for obstruction secondary to bladder cancer

Three studies (132 participants) reported very low quality evidence on percutaneous nephrostomy for the treatment of ureteric obstruction secondary to bladder cancer.

Improvement of renal function

One study (23 participants) reported that 18/23 (83%) patients improved to normal renal function after PCN (Ekici 2001).

Symptom relief

No evidence available

Treatment-related morbidity

The overall complication rate reported by three studies (Ekici 2003; Gupta 2007; El-Tabey 2005) was 20.2% (22/109), including PCN tube related complications and hematuria.

Overall survival

Three studies reported the rate of overall survival at follow-up, with 37/97 (38%) patients alive at mean follow-up ranging from 16-34 months. Median overall survival was 4.9 months (range 1-14) in one study (Ekici, 2001).

Subsequent chemotherapy

One study reported that 11/23 (48%) of patients underwent chemotherapy after PCN (Ekici, 2001).

Subsequent cystectomy

Three studies reported that 66/142 (46.5%) patients underwent cystectomy after PCN.

Health-related quality of life

No evidence available

Percutaneous nephrostomy for malignant obstruction

14 studies provided very low quality evidence on PCN for malignant obstructions.

Improvement of renal function

Six studies (795 patients) providing very low quality evidence reported a decrease in average serum creatinine levels after the PCN procedure. Two studies reported that 208/241 (86.3%) patients returned to normal renal function or showed a significant improvement after the procedure. In Pappas (2000), patients with gynaecological malignancy showed the best improvement rates.

Symptom relief

Relief of obstruction was reported in 151/248 (61%) patients (2 studies).

Treatment-related morbidity

11 studies reported an overall complication rate of 29% (447/1523).

Overall survival

Average overall survival was reported by eleven studies with length of survival ranging from 3.2 to 12.2 months across studies.

Subsequent chemotherapy

One study reported that 27 out of 38 patients (71%) underwent chemotherapy and/or radiotherapy after PCN (Meyer 1980).

Subsequent cystectomy

One study reported that 4 out of the 29 patients with bladder cancer in the cohort underwent cystectomy after nephrostomy (Fallon 1980).

Health-related quality of life

One study (270 patients) measured quality of life with the EORTC-QLQ and reported that there was no improvement in scores over the study period (Aravantinos 2007).

Percutaneous nephrostomy and retrograde stents for malignant obstruction

Seven studies reported the outcomes of patients who received PCN and those who received retrograde stents for malignant obstructions. All outcomes were assessed as being of very low quality.

Improvement of renal function

Three studies reported serum creatinine levels before and after interventions for malignant obstruction. Ku (2004) reported that both ureteral stenting and PCN resulted in a decrease of serum creatinine, with no significant difference between groups. Kanou (2007) reported that renal function improved in all patients and the average serum creatinine decreased after urinary diversion. Renal function was not reported separately for patients undergoing urinary stenting or nephrostomy. One study reported that serum creatinine increased in all patients, with a smaller elevation of creatinine levels in the PCN group (0.21 mg/dL) than in the stent group (0.78) (Chang 2012).

Symptom relief

One study of 110 patients reported that residual hydronephrosis after diversion was more common in the stent group than the PCN group (65% versus 27%) (Chang 2012).

Treatment-related morbidity

Four studies reported complications of PCN (n=218) and ureteral stents (n=156). Similar rates of complications were reported with ureteral stents (28.8%) and PCN (30.3%). A further study (Chang 2012) reported that the stent group had more frequent UTI, including urosepsis and pyelonphritis, than the PCN group, although this difference was non-significant.

Overall survival

Two studies reported overall survival in patients who underwent stenting and in those who underwent PCN. Average overall survival was 5.6 and 9.2 months for ureteral stents and 5.9 and 6.5 months for PCN. A further study reported an overall survival of 6.1 months for all patients regardless of the intervention received for ureteric obstruction. Multivariate analyses by Wong (2007) revealed that the

presence of metastases and a diagnosis of malignant obstruction in previously established malignancy were independent prognostic factors for inferior overall survival.

Subsequent chemotherapy

One study reported that 21% (11/52) of patients were treated with chemotherapy after successful drainage of the kidneys. It is not reported which intervention these patients received (Hubner 1993).

Subsequent cystectomy

One patient out of 30 with bladder cancer had a total cystectomy with urinary diversion for muscle-invasive disease after relief of obstruction in Chitale (2002).

Health-related quality of life

One study reported that responses to quality of life surveys were not significantly different for patients receiving nephrostomy tubes (n=16), double-J stents (n=15) or nephroureteral stents (NUS, n=15). Patients who had double J stents reported more pain, dysuria, and urinary frequency, compared with nephrostomy tubes and NUS at 30 and 90 days after placement.

Subcutaneous nephro-vesical/ nephro-cutaneous bypass for malignant obstructions

One study of 52 patients with metastatic disease undergoing palliative subcutaneous bypass was reported as a conference abstract only (Schmidbauer 2009). All outcomes were assessed as very low quality.

Improvement of renal function

Serum creatinine levels decreased from a mean of 6.1 to 1.55 mg/%.

Symptom relief

Preoperative hydronephrosis was completely eliminated in 80.8% of the renal units and was dramatically reduced in the remaining units.

Treatment-related morbidity

15/52 (28.8%) patients had UTI. 11 patients had a single and 4 patients recurrent UTI which resolved under antibiotics.

Overall survival

After a mean follow-up of 12.0 months (range 2-57) all but 4 patients had died from their progressive metastatic disease.

Health-related quality of life

On a range of 1 (very poor) to 10 (excellent), mean quality of life score was 3.6 (range 0-6) pre-operatively, and 7.8 (range 5-9) post-operatively.

No evidence available about subsequent chemotherapy and subsequent cystectomy

Evidence statements

Very low quality evidence was identified from 30 retrospective observational studies. All studies report an improvement of renal function and symptom relief in a majority of patients after PCN or stent placement. Seven studies reported the comparative outcomes of patients who received PCN and those who received retrograde stents for malignant obstructions. Ku *et al.* (2004) reported that both ureteral stenting and PCN resulted in a decrease of serum creatinine, with no significant difference between groups. One study reported that serum creatinine increased in all patients (n=110), with a smaller elevation of creatinine levels in the PCN group than in the stent group (Chang *et al.* 2012). This study also reported that residual hydronephrosis after diversion was more common in the stent group than the PCN group (65% versus 27%).

Four studies reported complications of PCN (n=218) and ureteral stents (n=156). Similar rates of complications were reported with ureteral stents (28.8%) and PCN (30.3%). A further study (Chang *et al.* 2012) reported that the stent group had more frequent UTI, including urosepsis and pyelonphritis, than the PCN group, although this difference was non-significant.

Two studies reported overall survival in patients who underwent stenting and in those who underwent PCN (Kanou *et al.*, 2007; Wong *et al.*, 2007). Average overall survival was 5.6 and 9.2 months for ureteral stents and 5.9 and 6.5 months for PCN.

One study reported that 21% (11/52) of patients were treated with chemotherapy after successful drainage of the kidneys. It is not reported which intervention these patients received (Hubner *et al.* 1993). In one study, 1/30 patients with bladder cancer had a total cystectomy with urinary diversion for muscle-invasive disease after relief of obstruction (Chitale *et al.*, 2002).

One study reported that responses to quality of life surveys were not significantly different for patients receiving nephrostomy tubes (n=16), double-J stents (n=15) or nephroureteral stents (NUS, n=15). Patients who had double-J stents reported more pain, dysuria, and urinary frequency, compared with nephrostomy tubes and NUS at 30 and 90 days after placement (Monsky *et al.*, 2013).

Table 174. GRADE evidence profile: Open nephrostomy, percutaneous nephrostomy, retrograde stents for malignant obstructions

Quality assessment							No of patients			Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Open nephrostomy	PCN	Retrograde stents	Relative (95% CI)	Absolute	
Improvement of renal function (assessed with: proportion with normal renal function 2 weeks after procedure)												
1[1]	observational study[2]	none	none	serious[3]	serious[4]	none	60/88 (68%) not reported separately by procedure			-	-	⊕OOO VERY LOW
Improvement of renal function (assessed with: proportion with improved renal function 2 weeks after procedure)												
1[1]	observational study[2]	none	none	serious[3]	serious[4]	none	21/88 (24%) not reported separately by procedure			-	-	⊕OOO VERY LOW
Symptom relief												
0	No evidence available											
Treatment-related morbidity												
1[1]	observational study[2]	none	none	serious[3]	serious[4]	none	8/14 (57%)	13/53 (24%)	5/27 (19%)	-	-	⊕OOO VERY LOW
Overall survival												
1[1]	observational study[2]	none	none	serious[3]	serious[4]	none	3.8 months	6.5 months		-	-	⊕OOO VERY LOW
Subsequent chemotherapy												
0	No evidence available											
Subsequent cystectomy												
0	No evidence available											
Health-related quality of life												
0	No evidence available											

[1] Zadra 1987
[2] case series
[3] Included patients with primary tumour sites other than the bladder
[4] Small sample size limits precision of the outcome

Table 175. GRADE evidence profile: Retrograde stents for malignant obstructions

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Retrograde stents		
Improvement of renal function (measured with: Change in serum creatinine level pre- and post-procedure (mg/dL))									
3[1]	observational studies[2]	serious[3]	none	serious[4]	none	none	N=313	Scr decreased in all studies by 34% to 57%	⊕OOO VERY LOW
Symptom relief (follow-up mean 11 months; assessed with: Success of retrograde stent - resolution of hydronephrosis and flank pain, or renal failure)									
1[5]	observational studies[2]	none	none	serious[4]	serious[6]	none	50/90 (55.6%)	-	⊕OOO VERY LOW
Treatment-related morbidity (assessed with: Overall complication rate e.g. catheter blockage, hematuria, UTI)									
3[1]	observational studies[2]	serious[3]	none	serious[4]	none	none	198/302 (65.6%)	-	⊕OOO VERY LOW
Overall survival									
4[7]	observational studies[2]	serious[3]	none	serious[4]	none	none	374	Average overall survival range 2.2 to 11.1 months (see Table 1)	⊕OOO VERY LOW
Subsequent chemotherapy									
1[8]	observational studies[2]	none	none	serious[4]	serious[6]	none	26/61 (42.6%)	-	⊕OOO VERY LOW
Subsequent cystectomy									
0	No evidence available								
Health-related quality of life									
0	No evidence available								

[1] Shekarriz 1999; Ganatra 2005; Kamiyama 2011
[2] case series
[3] In Shekarriz (1999) patients received either stent or nephrostomy, which were not reported separately
[4] Studies include patients with primary tumour sites other than the bladder
[5] Chung 2004
[6] Small sample size limits precision
[7] Shekarriz 1999; Ganatra 2005; Kamiyama 2011; Izumi 2011
[8] Izumi 2011

Table 176. GRADE evidence profile: Percutaneous nephrostomy for malignant obstructions secondary to bladder cancer

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Percutaneous nephrostomy		
Improvement in renal function (assessed with: Proportion improved to normal renal function)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	19/23 (82.6%)	-	⊕OOO VERY LOW
Symptom relief									
0	No evidence available								
Treatment-related morbidity (assessed with: Overall complication rate e.g. slippage of PCN tube, hematuria)									
3[4]	observational studies[2]	none	none	none	serious[3]	none	22/109 (20.2%)	-	⊕OOO VERY LOW
Overall survival (follow-up mean 16-34 months, range)									
3[4]	observational studies[2]	none	none	none	serious[3]	none	37/97 (38.1%)[5]	-	⊕OOO VERY LOW
Subsequent chemotherapy									
1[1]	observational studies[2]	none	none	none	serious[3]	none	11/23 (47.8%)	-	⊕OOO VERY LOW
Subsequent cystectomy									
3[4]	observational studies[2]	none	none	none	serious[3]	none	66/142 (46.5%)[6]	-	⊕OOO VERY LOW
Health-related quality of life									
0	No evidence available								

[1] Ekici 2001
[2] case series
[3] Small sample size limits precision
[4] Ekici 2003; Gupta 2007; El-Tabey 2005
[5] Median overall survival was 4.9 months (range 1-14) in Ekici 2001
[6] In El-Tabey 2005, 23/61 patients had inoperable locally advanced disease. 10/61 had palliative cystectomy without lymphadenectomy. 26/61 had radical cystectomy with intent to cure.

Table 177. GRADE evidence profile: Percutaneous nephrostomy for malignant obstructions

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCN		
Improvement in renal function (assessed with: Serum creatinine levels, Better indicated by lower values)									
6[1]	observational studies[2]	serious[3]	none	serious[4]	none	none	N=795	All studies reported a decrease in Scr after procedure	⊕OOO VERY LOW
Improvement in renal function (improved to normal function or significant improvement in function)									
2[5]	observational studies[2]	serious[3]	none	serious[4]	none	none	208/241 (86.3%)	-	⊕OOO VERY LOW
Symptom relief (assessed with: Relief of obstruction)									
2[6]	observational studies[2]	serious[3]	none	serious[4]	none	none	151/248 (60.9%)	-	⊕OOO VERY LOW
Treatment-related morbidity (assessed with: Complication rate - per person or per ureter)									
11[7]	observational studies[2]	serious[3]	none	serious[4]	none	none	447/1523 (29.3%)	-	⊕OOO VERY LOW
Overall survival									
11[8]	observational studies[2]	none	none	serious[4]	none	none	N=1299	Average OS ranged from 3.2 to 12.2 months	⊕OOO VERY LOW
Subsequent chemotherapy and/or radiotherapy									
1[9]	observational studies[2]	none	none	serious[4]	serious[10]	none	27/38 (71.1%)	-	⊕OOO VERY LOW
Subsequent cystectomy (assessed with: patients with bladder cancer undergoing surgery after nephrostomy)									
1[11]	observational studies[2]	none	none	serious[4]	serious[10]	none	4/29 (13.8%)	-	⊕OOO VERY LOW
Health-related quality of life (measured with: EORTC-QLQ; Better indicated by lower values)									
1[12]	observational studies[2]	none	none	serious[4]	none	none	270	No improvement in QoL	⊕OOO VERY LOW

[1] Meyer 1980; Ishioka 2008; Vehmas 1988; Lau 1995; Aravantinos 2007; Liatsikos 2009; [2] case series; [3] Patients with malignant and benign obstructions not reported separately in Vehmas (1988) and Pappas (2002) and complication rate not reported separately in Lau (1995); [4] Studies include patients with primary tumour sites other than the bladder; [5] Meyer 1980; Pappas 2000; [6] Vehmas 1988; Liatsikos 2009; [7] Meyer 1980; Ishioka 2008; Lienert 2009; Vehmas 1988; Lau 1995; Aravantinos 2007; Fallon 1980; Carrafiello 2006; Liatsikos 2009; Kinn 2003; Pappas 2000
[8] Radecka 2006; Lau 1995; Aravantinos 2007; Fallon 1980; Meyer 1980; Ishioka 2008; Watkinson 1993; Sheikh 2007; Lienert 2009; Kinn 2003; Pappas 2000; [9] Meyer 1980; [10] Small sample size limits precision; [11] Fallon 1980; [12] Aravantinos 2007

Table 178. GRADE evidence profile: Retrograde stent versus percutaneous nephrostomy for malignant obstructions

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Urinary stent	Percutaneous nephrostomy	Relative (95% CI)	Absolute	
Improvement of renal function (assessed with: Pre-procedure and post-procedure serum creatinine levels)											
3[1]	observational studies[9]	serious[2]	none	serious[3]	serious[5]	none	N=185	N=148	-		⊕OOO VERY LOW
Symptom relief (assessed with: Residual hydronephrosis)											
1[4]	observational studies[9]	serious[2]	none	serious[3]	serious[5]	none	43/66 (65.2%)	12/44 (27.3%)	RR 2.39 (1.43 to 3.99)	379 more per 1000 (from 117 more to 815 more)	⊕OOO VERY LOW
Treatment-related morbidity (assessed with: Overall complication rate)											
4[6]	observational studies[9]	none	none	serious[3]	serious[5]	none	45/156 (28.8%)	66/218 (30.3%)	-		⊕OOO VERY LOW
Overall survival											
2[7]	observational studies[9]	none	none	serious[3]	serious[5]	none	N=106 Average OS = 5.6 and 9.2 mo	N=71 Average OS = 5.9 and 6.5 mo	-		⊕OOO VERY LOW
Subsequent chemotherapy											
1[8]	observational studies[9]	none	none	serious[3]	serious[5]	none	11/52 (21.2%)		-		⊕OOO VERY LOW
Subsequent cystectomy (follow-up 10-34 months)											
1[10]	observational studies[9]	none	none	serious[3]	serious[5]	none	1/30 (3.3%)[11]		-		⊕OOO VERY LOW
Health-related quality of life											
1[12]	observational studies	none	none	none	serious[5]	none	N=15	N=16	No differences in QoL at 7, 30 or 90 days.		⊕OOO VERY LOW

[1] Ku 2004; Kanou 2007; Chang 2012; [2] Malignant and benign obstructions not reported separately in Chang 2012; [3] Studies include patients with primary tumour sites other than the bladder; [4] Chang 2012; [5] Small sample size / low number of events limits precision; [6] Ku 2004; Kanou 2007; Wong 2007; Hubner 1993; [7] Kanou 2007; Wong 2007; [8] Hubner 1993; [9] Case series; [10] Chitale 2002; [11] One patient out of 30 with bladder cancer had a total cystectomy with urinary diversion for muscle-invasive disease after relief of obstruction in Chitale (2002); [12] Monsky 2013

Table 179. GRADE evidence profile: Subcutaneous nephro-vesical/ nephro-cutaneous bypass for malignant obstructions

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subcutaneous nephro-vesical/ nephro-cutaneous bypass		
Improvement of renal function (follow-up mean 12.9 months; Better indicated by lower values)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	N=52[4]	-	⊕OOO VERY LOW
Symptom relief (follow-up mean 12.9 months; assessed with: Complete reduction of hydronephrosis)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	42/52 (80.8%)	-	⊕OOO VERY LOW
Treatment-related morbidity (follow-up mean 12.9 months; assessed with: UTI)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	15/52 (28.8%)	-	⊕OOO VERY LOW
Overall survival (follow-up mean 12.9 months)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	4/52 (7.7%)	-	⊕OOO VERY LOW
Subsequent chemotherapy									
0	No evidence available								
Subsequent cystectomy									
0	No evidence available								
Health-related quality of life (follow-up mean 12.9 months; measured with: 0=very poor, 10=excellent; range of scores: 0-10; Better indicated by higher values)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	N=52[5]	-	⊕OOO VERY LOW

[1] Schmidbauer 2009 (abstract only); [2] Case series; [3] Small sample size limits the precision of this outcome; [4] Mean serum creatinine decreased from mean of 6.1 (range 2.3-12.8) to 1.55 (range 0.55-6.3) mg/%; [5] Mean quality of life score was 3.6 (range 0-6) pre-operatively, and 7.8 (range 5-9) post-operatively

Table 180. Summary of results of studies on retrograde stent placement for malignant obstruction

Abbreviations: ON, open nephrostomy. PCN, percutaneous nephrostomy, Scr, serum creatinine, GI, gastrointestinal, Gynae, gynaecological, Uro, urological, NA, not available

Study (Study period)	N patients/ ureters	Primary malignancy	Type of stent	Successful stent insertion	Failure of stent function	Average survival time (range)	Renal function	Complications
Zadra 1987 (1978-1984)	88 Stent ON	Cervix 28% Prostate 17% Bladder 16%	NA	41%	NA	6.5 mo 3.8 mo	60/88 (68%) normal renal function, 21/88 (24%) improved significantly	13/53 (24%) PCNs (dislodgement, kinking, blockage, infection) 8/14 (57%) open nephrostomy (dislodgement, pulmonary embolus, infection/sepsis) 5/27 (19%) retrograde stenting (dislodgement, blockage, fractured stent)
Shekarriz 1999 (1986-1997) Stent +/or PCN	103	Prostate 30% Bladder 27% Colorectal 18.4%	NA	49%	51% required PCN after unsuccessful stent	3.7 mo (1-600 days)	Scr (mg/dL) Pre-op = 6.8 ±5.4 Post-op = 3.3 ±2.8	Overall 63/92 (68%). 63% minor (hematuria, catheter blockage, nephrostomy dislodgement). 5.4% major (significant bleeding, bladder tamponade)
Chung 2004 (1987-2002)	90	Colon 22% Breast 14% Rectal 13%	NA	95%	44%[9]	NA	NA	NA
Ganatra 2005 (1990-2004)	157	Ovarian 17% Lymphoma 11% Cervix 10%	Percuflex	84.7%	24%	11.1 mo (3 days-59.8 mo)	Pre-op = 2.51 Post-op = 1.43 57% decrease	110/157 (70%) total complications. 56/157 (36%) eventually referred for PCN due to stent failure. 14/157 pain/ lower urinary tract symptoms/hematuria. 8/157 stent migration requiring reoperation. 14/157 infection/urosepsis
Kamiyama 2011 (2002-2009)	53	GI 57% Prostate 6% Gynae 25%	NA	96%	31%	2.2 mo (1-546 days)	Scr (mg/dL) Pre-op = 3.09 (0.49-8.19) Post-op = 1.06 (0.40-6.59)	25/53 (47%) had at least one complication 30% catheter blockage with flank pain, followed by febrile UTI, hematuria, catheter migration
Izumi 2011 (2005-2010)	61/95	Gynae 34% Upper GI 21% Uro 16%	4.8/6-Fr Contour	78.7% Patients	21.8% Ureters	7.6 mo		No major complications. 39/61 (64%) had treatment after stent placement.

[9] Diagnosis of cancer, baseline creatinine greater than 1.30mg/dl and presence of post-stent systemic treatment (chemotherapy or radiation) were significantly associated with failure status

Table 181. Summary of results of studies on percutaneous nephrostomy for malignant obstruction

Abbreviations: ON, open nephrostomy. PCN, percutaneous nephrostomy, Scr, serum creatinine, GI, gastrointestinal, Gynae, gynaecological, Uro, urological, NA, not available

Study (Study period)	N patients/ ureters	Primary malignancy	Type of stent	Successful stent insertion	Failure of stent function	Average survival time (range)	Renal function	Complications		
El-Tabey 2005 (1990-2003)	61 – data available for 38 patients	Bladder 100%	NA	100%	NA	32% alive at average of 16.3 mo	NA	Septic shock 2/38 (5%)	Prolonged hematuria 2/38 (5%)	Slippage of PCN tube 1/38 (3%)
Meyer 1980 (1951-1976)	90	Cervical 49% Bladder 21%	NA	NA	NA	3.3 mo (1 day-4.5 yrs) Bladder=1.8 mo (1 day-4.6 yrs)	60/82 (73%) improved to normal renal function	Minor recurrent infection 4/90 (4%)	Tube needed repositioning within 30 days 3/90 (3%)	
Ishioka 2008 (1995-2007)	140	Gastric 21% Colorectal 24% Cervical 21%	8Fr	100%	NA	3.2 mo[10] (2 days-1,283 days)	Scr (mg/dL) Pre-op = 4.3 (0.54-18.57) Post-op = 1.1 (0.4-5.5)	Pyelonephritis 18/140 (13%)	Hematuria 11/140 (8%)	Dislodgement of catheter 27/140 (19%)
Watkinson 1993 (1981-1991)	50	Bladder 36% Cervical 32%	8.3 Fr Surgitech or Cook	NA	NA	Group2: 11.3 mo Group3: 11.1 mo Group4: 1.3 mo[11]	NA	NA		
Sheikh 2007 (1994-2006)	145	Prostate 34% Bladder 30% Cervical 17%	NA	NA	NA	Bladder: 12.2 mo Prostate: 11.6 mo Cervical: 11.9 mo	NA	NA		

[10] Low serum albumin before PCN (3 gm/dl or less), low grade hydronephrosis (grade 1 or 2), and large number of events related to malignant dissemination (3+) were associated with short survival

[11] Group 2 (n=16): untreated primary malignancy; Group 3 (n=8): relapsed malignant disease with viable treatment option; Group 4 (n=18): relapsed malignant disease with no conventional treatment option. All patients in Group 1 (n=8, non-malignant complication from previous surgery or radiotherapy) were alive at follow-up

Lienert 2009 (2005-2007)	49	Bladder 36% Prostate 30%	NA	NA	NA	5.8 mo (14-602 days)[12]	NA	Complication with PCN tube 19/49 (39%): Blockage (31 events), displacement (21 events), sepsis (11 events), haemorrhage (1 event), and pain requiring inpatient management (5 events).		
Gupta 2007 (1998-2005)	48	Bladder 100%	NA	NA	NA	16/36 (44%) died of progression after mean of 34 mo (12-80 mo)	NA	Overall complication rate 10/48 (21%) – 2 septicemic shock, 4 postobstructive dieresis, 3 hematuria, 4 slipping of the PCN.		
Vehmas 1988 (1978-1987)	158 (128 malignant)	Bladder 27% Gynae 17% Prostate 16%	Various models reported	91.7%	19%	NA	Scr (µmol/l) Pre-op = 614 1 wk Post-op= 346 1 mo Post-op=173	Major complications 10/181 (5.5%)	Minor complications 19/181 (10%): 5 UTI, 5 hematoma	
Radeckca 2006 (1998-2005)	151	Prostate 36% Bladder 28%	8.5 or 10.2 F	NA	7% (PCN dislocation) 11% (converted to alternative treatment)	All: 8.5 mo Bladder: 17.7 mo[13]	NA	NA		
Lau 1995 (1982-1992)	77	Cervical 55% Bladder 23%	NA	100%	NA	All: 26 wks Bladder: median = 2 years	Scr (µmol/l) Pre-op = 688 (70-1670) Post-op= 227 (60-1280)	Minor complications 20/77 (26%): 9 stent displacement or blockage	1 major sepsis causing death	
Aravantinos 2007 (1996-2003)	270	Bladder 20% Prostate 20% Gynae 20%	Foley	97.5%	NA	Bladder: (8-270 days) Prostate: (22-723 days)	Scr (mg/dL) Pre-op = 6.9 ±4.9 Post-op = 2.4 ±1.5	Minor temperature rise due to UTI 149/270 (55%)	Transfusion 8/270 (3%)	
Fallon 1980 (1966-1976)	100	Prostate 37% Bladder 29%	NA	NA	NA	Bladder: 4.5 mo		31 complications in 27/100 (27%) patients: 14 infections, 5 haemorrhage, 2 pulmonary embolus, 6 GI complications		
Carrafiello 2006 (2003-2006)	201/299 procedures	NA	8 Fr	100%	NA	NA	NA	Major complications 0/299	Minor complications 9/299 (3%) – 3 hematuria, 6	Tube complications 49/299 (16%)

[12] Low serum albumin level and events related to metastatic disease were indicative of poor prognosis

[13] Terminal bladder cancer (n=16) all died with a median OS of 61 days, range 4-628. Out of 27 patients with curable bladder cancer 21 were alive at end of follow-up.

								urine leakage		
Ekici 2001 (1987-2000)	23	Bladder 100%	NA	NA	NA	4.9 mo (1-14 mo)	19/23 (83%) improved to normal function **Scr (mg/dL)** Pre-op = 6 ± 5.1 Post-op= 1.6 ± 1.3	Overall complication rate = 7/23 (30%) 5/23 (22%) kinking of nephrostomy tubes 2/23 (9%) dislodgement requiring replacement		
Liatsikos 2009 (1996-2005)	90/119	Colon 26% Ovary 24% Uterus 24%	Self-expandable metal mesh 8mm	100%	48.8%	NA	Scr decreased to normal and hydronephrosis resolved 1-2 weeks after stent	Mild flank pain and discomfort 41/90 (46%)	Irritative bladder due to stent protrusion into bladder 5/90 (6%)	Recurrent UTI 3/90 (3%)
Kinn 2003 (1998-1999)	68	Prostate 56% Bladder 29%	NA	NA	NA	Prostate 7.9 mo (range 5 days-2.5 yrs) Bladder 5.3 mo (range 3 days-4 yrs)	NA	Perireneal hematomas 2/68 (3%)	Urosepsis 3/68 (4%)	
Pappas 2000 (1994-1998)	159 / 206 PCNs	NA (125 malignant, 30 benign)	8F	99%	NA	7.6 mo (2-685 days)	148/159 (93%) showed normalisation or significant improvement	Transfusion 3/159 (2%)	Hemorrhagic cystitis 1/159 (1%)	Dislodgement/obstruction of tube 15/159 (9%)

Table 182. Summary of results of comparative studies on retrograde stent placement versus PCN for malignant obstruction

Abbreviations: ON, open nephrostomy. PCN, percutaneous nephrostomy, Scr, serum creatinine, GI, gastrointestinal, Gynae, gynaecological, Uro, urological, NA, not available, hydrop, hydronephrosis

Study (Study period)	N patients/ ureters	Primary malignancy	Type of stent	Successful stent insertion	Failure of stent function	Average survival time (range)	Renal function	Complications
Ku 2004 (2000-2002)	68 stent	NA	7F/8F Percuflex	87.2%	11%	NA	**Decrease in Scr** 1.4 ± 0.4 g/L	Stent/catheter 8/68 (12%); Febrile episodes 10%; Acute pylonephritis 5.9%
	80 PCN			NA	1.3%		2.5 ± 0.2 g/L p=0.058	7/80 (9%); 15%; 3.8%
Kanou 2007 (1990-2003)	51 stent	Cervix 31% Rectal 23% Prostate 15%	6F C-Flex, Percuflex	72.5%	21.6%	5.6 mo	Scr (mg/dL) Pre-op = 4.9 Post-op = 1.1 100% recovered renal insufficiency	Early catheter replacement 5/29 (17%); Lower abdominal discomfort 2/29 (7%)
	24 PCN		14-Fr Malecot or balloon	NA	NA	5.9 mo		Accidental catheter withdrawal 9/46 (20%); Pain + dermatitis 3/46 (7%); Minor haemorrhaging 2/46 (4%)
Chitale 2002 (1998-2000)	65	Prostate 43% Bladder 46%	NA			NA	NA	1 patient had cystectomy and urinary diversion for MIBC
	24 stent			21%[14]	NA			
	60 PCN			95%	1.7%			
Wong 2007 (1991-2003)	102	Gynae 31% Uro 29% GI 21%	NA			6.8 mo	NA	Overall; Infection; Blockage; Haemorrhage
	25 stent				16%[15]	9.2 mo		14/25 (56%); 5/25 (20%); 8/25 (32%); 2/25 (8%)
	77 PCN				1%	6.5 mo		40/76 (53%); 27/77 (35%); 19/77 (25%); 2/77 (3%)
Chang 2012 (2003-2009)	66 stent	56/110 (51%) benign, 54/110 (49%) malignant mostly cervical[16]	7-Fr Inlay		9/86 (10%) converted to PCN due to failure	**Residual hydrop** 43/66 (65%)	**Change in Scr** 0.78 (-1.8 – 1.2) mg/dL	Stent group had more frequent UTI, including urosepsis and pyelonphritis, than the PCN group, although this difference was non-significant (numbers not reported).
	44 PCN					12/44 (27%) p=0.01	0.21 (-2.4 – 1.9) mg/dL p=0.003	
Hübner 1993 (1986-1989)	24 stent	Colon 29% Bladder 25%	NA	NA	NA	6.1 mo (all	NA	Flank pain 8/34 (24%); Dysuria 7/34 (21%); Stent dislocation 1/34 (3%)

[14] Low success of retrograde stenting due to inability to cannulate the ureteric orifices due to trigonal distortion or failure to negotiate the lower segment ureter in 17/19 (89%) patients

[15] All failures with primary retrograde stents occurred in prostate or bladder cancer

[16] Malignant and benign obstructions not reported separately

28 PCN	Cervical 17%	patients)	Accidental tube dislodgement 5/16 (31%)

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Evidence tables

Abbreviations: BCa, bladder cancer; PCN, Percutaneous nephrostomy; RC, radical cystectomy

Study	Participants, age, gender	Participant characteristics	Intervention	Length of follow-up	Outcomes	Additional comments
El-Tabey 2005 **Retrospective review** **Egypt**	N=61 Mean age = 41.2 ± 12.5, range= 35-63 years 69% M / 31% F	1990- 2003 - Patients with BCa causing ureteral obstruction. Mean serum creatinine at presentation=11.4± 5.1, range 4.3 to 22.5. 7 patients had severe metabolic acidosis with hyperkalemia necessitating urgent haemodialysis. 95% invasive BCa, 8% ureteral invasion by tumour	All 61 patients underwent insertion of an ultrasound guided PCN tube with broad spectrum antibiotic coverage, aiming at a maximum drop on creatinine and improvement of patient's general condition. Bilateral PCN tubes were fixed starting with the better functioning side. After stabilization of kidney function, all patients underwent local tumour staging and metastatic workup. 23 patients with inoperable locally advanced bladder tumours (invading pelvic wall or rectum) were discharged with permanent PCN tubes and no further follow-up data were available. 34 patients had stage T3b or T4a bladder mass. 6 had evidence of N1 disease.	Range 8-134 months, mean 14.2 ± 9.1 months	Complications of PCN tubes, Subsequent cystectomy rates, Overall survival	
Meyer 1980 **Retrospective review** **USA**	N= 90 Gender and age not reported	1951-1976 - Patients with presumed advanced malignancy and bilateral ureteral obstruction (1951-1976). Mild to marked bilateral hydronephrosis and hydroureter in all patients except two who had prior unilateral nephrectomy. 62/90 (69%) had no visible function of at least one kidney. In 66/90 (73%) had blood urea values of 100 mg/dl or greater. 44/90 (49%) cervical cancer, 19/90 (21%) bladder cancer	83 patients underwent unilateral nephrostomy, 1 patient had bilateral nephrostomy, 3 unilateral skin ureterostomies, 3 ileal loop diversions.		Survival Complications Subsequent treatment	
Ishioka 2008 **Retrospective review** **Japan**	N=140 Median age 57 (31-85) 43% M / 57%	Between 1995-2007 patients with obstructive nephropathy secondary to advanced incurable malignant cancer. All presented with renal failure. 5 patients (4%) had no therapy before diversion. 25/110 (18%) grade 1-2 hydronephrosis, 115/140 (82%) grade 3-4 hydronephrosis. Malignancy type: 29/140 (21%) gastric, 34/140 (24%) colorectal, 30/140 (21%) cervical, 13/140 (9%) urothelial.	PCN insertion under local anaesthesia guided by ultrasonic and fluoroscopic imaging. After percutaneous puncture of the kidney with patient in the prone position, the Seldinger technique was followed to access the pelvicaliceal system and a 8Fr nephrostomy pigtail catheter was left in situ. PCN tube placement was unilateral in all patients. In the presence of bilateral obstruction the PCN tube was inserted on the side with good preservation of renal parenchymal width as confirmed by ultasonography	Not reported	Result of PCN, Overall survival.	Bladder cancer not stated. Prognostic model stratified patients into 3 risk groups.
Lienert 2009 **Retrospective review** **New Zealand**	N=52 (49 in final analysis) Median age 71 (36-91) 55% M/ 45% F	2005-2007 – All patients who had PCN tubes inserted due to malignant obstruction. 15/49 (30%) prostate, 18/49 (36%) bladder, 6/49 (12%) colorectal	Bilateral nephrostomy tubes were inserted in 23/49 (46%) patients.	Not reported	Overall survival, Complications	Validation of Ishioka prognostic risk groups.
Watkinson 1993	N=50	Patients with a history of abdominopelvic	All PCN procedures performed under local anaesthesia	Minimum 99	Overall survival	

Study	Participants, age, gender	Participant characteristics	Intervention	Length of follow-up	Outcomes	Additional comments
Retrospective review **UK**	25/50 (50%) Male, mean age 57 years 25/50 (50%) Female, mean age 48 years	malignancy who had undergone PCN (1981-1991). 18/50 (36%) primary bladder tumour, 16/50 (32%) cervical tumour. Patients classified into 4 groups based on cause of renal tract obstruction. Group1 (n=8): non-malignant complication from previous surgery or radiotherapy Group2 (n=16): untreated primary malignancy Group3 (n=8): relapsed malignant disease with viable treatment option Group4 (n=18): relapsed malignant disease with no conventional treatment option	using an 8.3 French pigtail catheter (Surgitech or Cook), utilizing screening facilities or grey scale ultrasonography and with routine antibiotic cover. All procedures performed by one of two operators.	days on each surviving patient		
Sheikh 2007 **Retrospective review** **UK**	N=145 Age/gender not reported	1994-2005 – patients underwent PCN and subsequent antegrade stenting for obstructive uropathy in pelvic malignancies , either at same time or a later date. Primary malignancy: 49/145 (34%) prostate, 44/145 (30%) bladder, 24/145 (17%) cervical/uterine.	145 patients had 241 stents inserted. 37/45 (26%) had simultaneous PCN and antegrade stenting. 108/145 (74%) had delayed stenting. 38/145 (26%) had unilateral stenting.	Not reported	Survival	Abstract only
Gupta 2007 **Retrospective review** **India**	N=58 Mean age 58 ±9.2 (range 42-78) Gender not reported	1998-2005 patients with stage T2 or higher bladder cancer and obstructive uropathy. Mean Scr at presentation was 9.2 ±4.5 mg% (range 2.4 – 16.5). 2 patients had immediate haemodialysis (HD) and refused further treatment, 8 underwent RC without PCN or HD. 10 patients required urgent HD before PCN. 38 underwent PCN directly. 2 died after PCN due to progressive sepsis and multi-organ failure	PCN was done under ultrasound guidance with broad spectrum antibiotic coverage. In patients with bilateral obstruction PCN was done on each side simultaneously to achieve rapid decrease in Scr. After nadir Scr was achieved bimanual examination and radiological imaging was performed for local staging and metastatic assessment. 14 patients had locally inoperable or metastatic disease or Scr failed to improve significantly. These patients were discharged with a permanent nephrostomy catheter. In these patients the standard 10Fr catheters were replaced with 18 Fr Foley catheters.	Mean 34 months (12-80)	Cystectomy PCN complications Renal function	
Vehmas 1988 **Retrospective review** **Finland**	N=181 (128 malignant) Mean age 64 (15-84) 50% M/ 50% F	1978-1987 -Two-thirds were cancer patients with urinary obstruction from primary or metastatic neoplasm. 35/128 (27%) bladder cancer, 22/128 (17%) gynaecological cancer, 20/128 (16%) prostate. Hydronephrosis diagnosed in 147 patients.	PCN - Atropine, diazepam and if needed i.v. analgesics were given as premedication. Puncture guidance initially based on fluoroscopy but later ultrasound was used. 3-day dilation was replaced by instant dilation to the intended size of the catheter. Different models of catheter were tried including straight or pigtail, Malecot catheters and balloon catheters. 15/181 (8.3%) could not be catheterised at all. Not all patients were followed up for Scr levels.	Not reported	Success of stents Complications Creatinine levels	Outcomes not reported separately for malignant/ benign obstructions
Radecka 2006 **Retrospective review**	N=151 Mean age 73 (51-97)	1998-2005 - Patients with malignancies causing obstruction referred for treatment with PCN. 55/151 (36%)	Bilateral PCN was performed in 42 patients. PCN performed under local anaesthesia and antibiotic cover. The kidney was punctured percutaneously and the	Median 3 years 9 months (range 1 yr 3	Survival	

Study	Participants, age, gender	Participant characteristics	Intervention	Length of follow-up	Outcomes	Additional comments
Sweden	74% M / 26% F	prostate cancer, 43/151 (28% bladder, 11/151 (7%) gynaecological, 16/151 (11%) colorectal. 16/43 (37%) terminal bladder cancer, 27/43 (63%) curable bladder cancer	Seldinger technique was followed to access the pelvo-calyceal system under ultrasonic and fluoroscopic guidance. After dilation an 8.5 or 10.2 F nephrostomy tube was left in situ.	months to 7 yrs)		
Lau 1995 **Retrospective review** **UK**	N=77 Mean age 56 (24-78) 32% M / 68% F	1982-1992 – patients with newly diagnosed or previously treated pelvic malignant disease and evidence of hydronephrosis with impaired renal function. 42/77 (55%) cervical cancer, 18/77 (23%) bladder cancer. Group1 (n=31): patients with untreated primary malignant disease Group2 (n=15): recurrent malignant disease for which further treatment was available Group3 (n=12): recurrent malignant disease with no further treatment available Group4 (n-19): benign complications from previous treatment.	PCN performed under local anaesthesia with fluoroscopic or ultrasonographic guidance. Patients treated with JJ stents not included although some patients had undergone failed attempts at retrograde stenting before PCN. PCN was successfully inserted in all patients.	Not reported	Survival, changes in serum creatinine Complications	Complications not reported separately for malignant and benign obstructions.
Aravantinos 2007 **Retrospective review** **Germany/Greece**	N=270 Mean age 63 (40-86) Gender not reported	1996-2003 – patients with obstructive nephropathy caused by advanced malignancy who underwent PCN. Uremia was the main presenting symptom in 88% of participants, 12% oligoanuria. 92% bilateral obstruction. 22/270 (8%) had a solitary functioning hydronephrotic kidney. 54/270 (20%) in each group of bladder cancer, prostate, gynaecological, colorectal cancer, and 'other' including gastric, pancreatic, lymphomas. Group A: locally extended malignancy affecting the urinary system Group B: largely disseminated disease that produced obstructive nephropathy including patients with enlarged lymph nodes and distant metastases	The technique of percutaneous approach was identical in all cases. The side of nephrostomy was chosen based on parenchymal thickness demonstrated by ultrasonography. Retrograde stenting was either unsuccessful or not attempted because of anticipated complicated anatomy. PCN under local anaesthesia under ultrasonographic and fluoroscopic guidance. Initial puncture made with 17.5 gauge Chiba needle with removable trocar (usually with a free-hand technique). Then contrast was injected to confirm correct placement of the needle. A 0.035-inch Lunderquist inflexible steel guide wire with flexible tip was then inserted into the collecting system. A series of Alken metal dilators inserted over this guidewire produced a channel of up to 14 to 16F in diameter. Removed all but the initial dilators; an open-ended silicone Foley catheter was advanced over it into the pelvis and eventually removed. Catheters usually changed every 3 months.	Not reported	Overall survival Quality of life (EORTC QLQ) Creatinine levels	
Carrafiello 2006 **Retreospective review** **Italy**	N=201 (299 procedures) Mean age 66 (32-102)	All patients affected by prior malignancy. 44/299 (15%) severe (grade IV) hydronephrosis, 255/299 (85%) grade II-III hydronephrosis. 68/299 (23%) emergency procedures due to rapid worsening of renal function.	149 PCNs were on the right side and 88 on the left side. 31 patients underwent bilateral PCN. All patients had normal pre-procedure coagulation and platelet estimation. PCN under ultrasound and fluoroscopic guidance, with haemodynamic monitoring. 271/299 (91%) only local anaesthesia was used at the site of	Not reported	Complications	

Study	Participants, age, gender	Participant characteristics	Intervention	Length of follow-up	Outcomes	Additional comments
	54% M / 46% F		puncture. 28/299 (9%) i.v. sedoanalgesia was necessary to due lack of collaboration or excessive pain. 255/299 (85%) Seldinger technique, 15% one-step technique used when excretory system was very dilated (grade IV hydronephrosis). All patients received prophylactic antibiotic regimen beginning immediately before procedure and continuing for the following 4 days. 100% immediate success was obtained.			
Fallon 1980 **Retrospective review** **USA**	N=100 Age range 15-84 65% M/ 35% F	Patients with upper tract obstruction associated with invasive, incurable cancer. 37/100 (37%) prostate, 29/100 (29%) bladder, 15/100 (15%) cervical. 71 patients were azotaemic at the time of nephrostomy (blood urea >15mmol/l). 76 bilateral obstruction, 15 unilateral. 6/15 had solitary kidneys. In 80 patients some form of therapy for the primary malignancy had been given prior to the need for nephrostomy.	8 patients had emergency treatment. In 60 cases unilateral nephrostomy was performed and in 40 patients bilateral nephrostomy was done, either simultaneously or sequentially. Patients were categorised for quality of survival Group A: Patient discharged home from hospital. Little or no pain and survival of at least 2 months. Patient was generally ambulatory and alert Group B: Patient was discharged home or to a minimal care institution. Pain controlled with analgesics and there was at least a moderate limitation of activities. Group C: Patient confined to hospital requiring narcotics for pain, or a continuing decline in status.	Not reported	Survival Creatinine Quality of survival	
Ekici 2001 **Retrospective review** **Turkey**	N=23 Mean age 55 (25-76) 91% M/ 9% F	1987 -2000 - Consecutive patients who underwent PCN for ureteral obstruction associated with bladder cancer. 10 presented with oliguria, anuria, UTI or renal damage. 17 patients reported flan or abdominal pain. PCN performed in 3 patients who had recurrent malignant obstruction after cystectomy. 17 patients underwent primary PCN.	PCN performed according to standard techniques under local anaesthesia. 11/23 (48%) had unilateral obstruction. 12/23 (52%) had bilateral obstruction.	Not reported	Overall survival Creatinine Complications	
Liatsikos 2009 **Retrospective review** **Greece**	N=90 Mean age 59 (35-80) 38% M / 62% F	From 1996-2005, patients with unilateral or bilateral extrinsic malignant ureteral obstruction secondary to tumours associated with pelvic or retroperitoneal metastasis in all cases. Obstruction was related to compromised renal function, hydronephrosis and/or UTI. Primary site of disease: colon 31 ureters, ovary 29 ureters, uterus 24 ureters, prostate 22 ureters, bladder 9 ureters	Metal stents were placed percutaneously under fluoroscopic guidance through a nephrostomy tract in all cases. Antibiotic prophylaxis given 24 hours before intervention. The standard procedure for PCN was used. A 7Fr long sheath was placed in the dilated ureter to facilitate a hydrophilic guidewire through the stricture. Obstruction dilated with 6-7mm wide angioplasty balloons then standard vascular self-expandable metal stents with 8mm diameter and length of 3-12cm were applied.	1 year. Median follow-up 15 months (8 to 38)	Renal function Successful abolishment of stricture	Study was an off label application and stent brands chosen according to availability
Kinn 2003 **Retrospective review**	N=68 Age/gender not reported	1998-1999 68 patients with malignancy underwent PCN. The most common indication for PCN was uremia followed by hematuria and urosepsis.	A unilateral nephrostomy was usually chosen, and if the creatinine level had not dropped within 3-4 days, a catheter was introduced in the other kidney as well.	Not reported	Survival Complications	

Study	Participants, age, gender	Participant characteristics	Intervention	Length of follow-up	Outcomes	Additional comments
Sweden		38/68 (56%) prostate cancer, 20/68 (29%) bladder cancer. All prostate cancer patients were receiving hormone therapy or had ablation of testes at the time of PCN				
Ganatra 2005 **Retrospective review** **USA**	N=157 Mean age = 54.7 (23-83) 39% M / 61% F	All patients who underwent ureteral stent placement for noncalculous reasons. Direct tumour obstruction by bladder cancer was excluded. Extrinsic ureteral compression from bladder cancer lymphadenopathy was included. Patients with extrinsic ureteral compression and direct tumour invasion into the bladder from other malignancies were included. Average creatinine before stent was 2.51. Majority ovarian cancer. 2/157 bladder cancer	Retrograde internal ureteral stents were attempted in all patients (n=157) with evidence of malignant ureteral obstruction. Failure defined as an inability to place stents, or recurrent ureteral obstruction despite stent placement (increase in creatinine by 50%, or nadir, pain, infection, or hydronephrosis). Immediate failure of stent (impossible to place stent due to external compression) referred for PCN.	Mean = 13.6 months, range = 1 day to 84.3 months	Stent failure rate – immediate vs. Late failure, Progression to PCN Creatinine level, Mortality rate,	
Izumi 2011 **Retrospective review** **Japan**	N=61 Median age 64 (27-89) 31% M/ 69% F	Patients who underwent retrograde ureteral stenting for malignant ureteral obstruction (2005-2010). 21/61 (34%) gynaecologic cancers, 13/61 (21%) upper GI, 10/61 (16%) urological cancers, bladder cancer n=2.	Retrograde ureteral stent placement under x-ray guidance. Multi-length ureteral stents of 4.8 or 6Fr (Contour) were used. Interval between stent changes were initially planned at 3 months.		Overall survival Stent-failure free survival Stent-related complications	
Chung 2004 **Retrospective review** **USA**	N=101 Mean age 61 (33-90) 44% M / 56% F	Patients with extrinsic ureteral obstruction – defined as presence of confirmed hydronephrosis, and the presence of flank pain, or increased serum creatinine, or both symptomology and increased creatinine. Patients without hydronephrosis were excluded. 64/101 (63%) unilateral involvement, 37/101 (37%) bilateral involvement. 90/101 (89%) malignant cause, 11/101 (11%) benign cause. Majority colon and rectal cancer. 2 bladder cancer patients	Retrograde placement of internal ureteral stents. Data used for the first stent only for those with bilateral obstruction. Patients who underwent antegrade ureteral stent insertion after initial management with PCN were excluded. Stent failure was defined as persistent hydronephrosis with flank pain or persistently increased serum creatinine levels. Impossibility of stent placement due to severe external compression was also considered failure. PCN tubes were placed in 27 (27%) patients due to retrograde stent failure.	Mean 11 months, range 0-127	Stent failure/success	
Kamiyama 2011 **Retrospective review** **Japan**	N=53 Mean age 61 (32-92) 42% M/ 58% F	2002- 2009 - Patients who underwent retrograde ureteral stenting to decompress malignant extrinsic ureteral obstruction. 2/53 patients had antegrade stenting because it was impossible to identify the ureteral orifices. 30/53 (57%) GI cancer, 3/53 (6%) prostate, 13/53 (25%) gynaecological. 8/53 (15%) direct tumour invasion to the bladder, 18/53 (34% peritonitis carcinomatosa, 15/53	Ureteral stenting indicated when obstruction was suspected from imaging studies. PCN selected for the patient with direct invasion of the bladder or prostate cancer, and those in poor general condition. Stent insertion was performed using a caudal block under fluoroscopic guidance. One stent was inserted per ureter without dilations of the obstructive lesion. All stents generally exchanged every 3 months. All ureteral stents were of same hydro plus coating material.	Mean 106 days (1-1627)	Stent failure – inability to place stent or recurrent obstruction. Renal function Survival	

Study	Participants, age, gender	Participant characteristics	Intervention	Length of follow-up	Outcomes	Additional comments
		(28%) local recurrence, 13/53 (24%) lymph node metastases.				
Shekarriz 1999 **Retrospective review** **USA/Germany**	N=103 (92 bilateral, 11 unilateral Median age 68 ± 12.5. Patients with bladder/ prostate cancer were significantly older. Gender not reported	Patients who underwent palliative urinary diversion (stent or PCN) for ureteral obstruction secondary to advanced malignant disease (1986-1997). 28/92 (30%) primary prostate malignancy, 25/92 (27%) bladder, 19/92 (21%) GI, 20/92 (22%) gynaecological. 14/92 (15%) had no prior therapy at time of diversion – 7 of these were deemed incurable	Endoscopic ureteral stent placement or PCN were performed according to standard techniques.		Creatinine levels, Survival, Complications, Performance status	Outcomes for stent or PCN not reported separately. Bilateral and unilateral reported seperately
Chitale 2002 **Retrospective review** **UK**	N=65 Age range 53-84 years 80% M / 20% F	Patients with upper tract obstruction secondary to malignant pelvic disease. 28/65 (43%) primary prostate cancer, 30/65 (46%) bladder cancer. 46/65 (71%) renal impairment, 19/65 (29%) normal renal function. 47/65 (72%) bilateral hydronephrosis, 28% unilateral hydronephrosis. In total 105 renal units needed decompression.	Endoscopic retrograde stenting was attempted in 24/65 (37%) patients as the primary method of decompression. PCN offered to 41/65 (63%) patients. In 19/24 (79%) patients in whom retrograde stenting failed were offered PCN. Patients with nephrostomy inserted either as primary or secondary treatment procedure went on to have an antegrade stent inserted within a week of nephrostomy insertion. A second puncture was made when necessary. If the initial nephrostomy was placed in the lower calyx, a mid-calyceal puncture was performed to facilitate antegrade insertion of stent	Range 10 months to 3 years	Success/failure of stenting, mortality	Successful stenting not defined
Chang 2012 **Retrospective review** **Taiwan**	N=110 Mean age 64 years (19-89). Younger patients in ureteral stent group 43% M/ 57% F	2003-2009- 110 patients with need for unilateral or bilateral upper urinary tract diversion for at least 6 months. 56/110 (51%) benign causes, 54/110 (49%) malignant causes – mostly cervical cancer. 3 bladder cancer patients. Mean baseline serum creatinine level was higher in PCN than stent group (2.96 vs. 1.48 mg/dL). Cases of stone-related hydronephrosis were excluded.	66/110 (60%) patients with ureteral stents (86 renal units). 44/110 (40%) with PCN tubes (60 renal units). <u>Stent group:</u> 7-Fr catheters (InLay ureteral stents) under cystoscopy. <u>PCN group:</u> Radiologists performed procedure under ultrasonographic guidance. In all cases 8-Fr nephrostomy catheters were put in place. Both PCN tubes of double-J stents were kept for a maximal period of 3 months, and then replacement was required. Tubes also replaced when obstructions or infections were observed.	Not reported	Serum creatinine level, hydronephrosis,	Results for benign and malignant obstruction not reported separately
Zadra 1987 **Retrospective review** **Canada**	N=135 with unilateral (37) or bilateral (98) malignant ureteral obstruction Average age at diagnosis = 59 years 42% M / 58% F	Bilateral group: Average creatinine = 689µmol/L. Five patients lost to follow-up and five refused treatment and died within 25 days. 88 patients available for analysis. 72% pelvic malignancy (28% cervix, 17% prostate, 16% bladder).	From 1978-1981 half of the 31 patients were treated with open nephrostomy (ON). From 1982-1984 the majority of the 62 patients underwent nonoperative urinary diversion with no open nephrostomies performed. Overall 37 PCN, 23 retrograde stenting (RS), 7 antegrade stenting, 14 open nephrostomy, 8 ileal conduit, 3 cutaneous ureterostomies, 1 ureterolysis. There was no attempt to remove internal stents or permanent nephrostomy tubes	Not reported. Mean survival time for tumour type reported after at least 8 month follow up.	Renal function Survival	Diversion by RS difficult in prostatic and bladder tumours because the ureteral orifices were difficult to see or were grossly invaded by the tumour

Study	Participants, age, gender	Participant characteristics	Intervention	Length of follow-up	Outcomes	Additional comments
Hübner 1993 **Retrospective review** **Austria**	N=52 Median age 67 (43-81) 40% M/ 60% F	Patients with malignant ureteral obstruction. 15/52(29%) primary colon cancer, 13/52 (25%) bladder cancer, 9/52 (17%) cervical, 6/52 (12%) ovarian, 4/52 (8%) prostate. Indications for diversion were hydronephrosis at least grade II in all cases.	24 patients primarily treated with retrograde implantation JJ stents through the cytoscope, 28 patients PCN tubes was first therapy. In cases of unsuccessful attempted retrograde stenting a PCN tube was placed. In cases of acute deterioration of renal function due to hydronephrosis, leucocytosis, nausea, vomiting or fever, a PCN was placed primarily for reliable control of urinary output. In patients with incontinence due to either tumour dependant lower urinary tract fistulas or severe dysuria caused by tumour infiltration of the bladder, percutaneous occlusion of the ureter was performed. No general anaesthesia was required. Either local anaesthesia or intravenous sedation used. In 12 patients PCN were changed to different urinary diversions.	29 patients observed for an average 11.8 months, range 4.7-25.7 months. 25 patients followed to death for average survival of 6.1 months, range 0.3 to 13.5 months	Positive result defined as discharge from hospital for at least 8 weeks without permanent need for analgesics	
Ku 2004 **Retrospective review** **Korea**	N=148 Mean age 57 (20-84) 45% M / 55% F	All patients who underwent palliative urinary diversion for ureteral obstruction secondary to advanced malignant disease (2000-2002). Hydronephrosis detected in all patients. 20/148 (13.5%) had co-morbid diseases including hypertension, diabetes, hepatitis etc. Baseline serum creatinine =2.6 ±0.4 g/L for the IUS group versus 4.5 ± 0.6 g/L for the PCN group (p=0.003)	68 retrograde internal ureteral stent (IUS), 88 PCN tube placement. The IUS was 7F to 8F and 22cm-26cm long (Percuflex). Total indwelling period ranged from 1-42 months (mean 6.0). During follow-up the IUS or PCN tube was changed regularly in most patients, mean interval between changes was 2 months (range, 1-5). The indwelling duration and interval of change in the IUS group was significantly longer than in the PCN group.	6 months	Stent failure defined as clinical stent occlusion, recurrent episodes of acute renal colic or persistent or progressive hydronephrosis. Complications	Site of primary tumour site not reported
Wong 2007 **Retrospective review** **Australia**	N=102 Median age 62 (31-86) 44% M/ 56% F	1991-2003 - Patients who underwent decompression for malignant ureteral obstruction. 77/102 (75%) PCN, 25/102 (25%) retrograde stent. 60/102 (59%) had known metastases. 77/102 (75%) prior therapy. 39/102 (38%) preop creatinine >40. 32/102 (31%) gynaecological cancer, 30/102 (29%) urological cancer, 21/102 (21%) GI cancer. Median time for obstruction to develop from diagnosis of primary malignancy was 11 months (0-345)	Radiological antegrade stent, retrograde stent, or PCN were performed according to standard techniques by consultant urologists and radiologists. The choice of procedure first attempted was directed by patient factors (fitness for anaesthesia, bladder tumour obviating RS) and by institutional factors (availability of facilities). Antegrade stenting followed PCN when feasible. Failure of the procedure means urinary decompression was not achieved. Three patients who failed retrograde stenting went on to undergo successful PCN insertion. Internalization with antegrade stenting (AS) was attempted in 37/77 (48%) who had PCN. The other 32 patients were too unwell or died before AS. AS was successful in 21/37 (57%) defined as the patient no longer being dependant on a covering PCN.	Median 46 months	Overall survival Complications Failure of procedure	
Kanou (2007) **Retrospective review** **Japan**	N=75 Mean age 63 (36-90) 40% M / 60% F	1990-2003 – Secondary ureteral obstruction due to retroperitoneal or pelvic invasion of malignant disease. 23/75 (31%) cervical cancer, 17/72 (23%) rectal, 11/75 (15%) prostate, 4/75 (5.3%)	Obstructed ureters were stented retrogradely with 6-Fr double J catheters C-Flex or Percuflex (n=51). Those double-J catheters were custom made without venting side holes. Nephrostomies (n=24) were done percutaneously under ultrasonographic guide with either	Mean 5.7 months (5 days – 19 months)	Success of procedure Renal function Survival	

Study	Participants, age, gender	Participant characteristics	Intervention	Length of follow-up	Outcomes	Additional comments
		bladder. Cases with normal urinary excretion from one kidney was excluded.	14-Fr Malecot catheter or a nephrostomy balloon catheter. These procedures were done in the bet ter functioning kidneys unilaterally. Most procedures done under epidural, spinal or local anaesthesia. Anaesthesia time for stenting was 41.2 mins, and 48.8 mins for PCN. 37/51 (73%) stents were successful. 14 failed stents were given PCN. A further 8 patients received PCN due to unsuccessful maintenance of stents.			
Pappas (2000) **Appears prospective** **Greece**	N=159 Mean 65.1± 15.9 (18 -94) 64% M / 36% F	1994-1998 – 159 patients presenting with obstructive uropathy. 125 patients had malignant obstruction, 30 patients had benign causes. 114 patients had previous unsuccessful retrograde stent.	All PCNs performed in the radiology department under local anaesthesia. The Seldinger technique was used to access the pelvicaliceal system percutaneously under ultrasonic and fluoroscopic guidance in 154 patients. In 84 patients two different punctures were performed, one with 22-guage needle to opacify the pelvicaliceal system and the other using an 18-guage needle to insert a 0.0035-inch guidewire, dilate to 8F to 10F, and place the nephrostomy tube (8F in most) and the double J-catheter when needed. In 75 patients, the initial puncture was also used for the subsequent procedure. 39/48 (81%) had successful antegrade stent insertion.	Not reported	Renal function Survival Complications	Renal function and complications not reported separately for malignant and benign obstructions.
Schmidbauer 2009 **Appears prospective** **Austria**	N=52 Age/gender not reported	1999-2008 – patients with end-stage metastatic malignant disease had palliative diversion (in 12 nephrocutaneous bypass)	Subcutaneous nephro-vesical/ nephro-cutaneous bypass. For a subcutaneous bypass two F12 polyurethane tubes are placed as nephrostomy and cystostomy and connected subcutaneously. In patients with impaired bladder function the distal end of the system is diverted percutaneously in the lower abdomen to simply drain into a urostomy bag. 8/52 (15%) system had to be replaced due to occlusion after a mean 9.8 months.	Mean 12.9 months (2-57 months)	Renal function, quality of life (0=very poor, 10= excellent)	Abstract only
Monsky 2013 **Prospective longitudinal study** **USA**	N=45 consecutive patients 19 male, 24 female	Consecutive patients with malignancy-related ureteral obstruction. 14 bladder cancer, 4 prostate, 13 cervical.	Nephrostomy tubes (8.5F) – 24 tubes in 15 patients (9 bilateral and 6 unilateral), double J stents (8.5F, 22-26cm) (24 stents in 15 patients, 9 bilateral and 6 unilateral), or internal external nephroureteral stents (8.5F, 22-26cm) – 22 stents in 15 patients. Choice of tube determined by MDT. 13 patients were lost to follow-up.	90 days	Quality of life: FACT-BL Assessment of urinary symptoms. Measured at 7, 30 and 90 days after placement.	No baseline QoL measure. Number of participants in final analysis unclear.

5.2.3 Intractable haematuria

Review question: What specific interventions are most effective for patients with incurable bladder cancer and intractable bleeding?

Rationale

Intractable bleeding from the bladder is one of the most serious terminal complications for patients with bladder cancer because it is difficult to manage; it is frightening for the patient and their carers and almost certainly means that the patient will have to be admitted to hospital for management. Intractable bladder bleeding may occur before the patient is in a terminal phase but it may be the terminal event for bladder cancer patients. This means that they may die in hospital and certainly may lose precious hours and days that they would have rather spent at home with their family.

Severe bleeding can arise from the bladder cancer itself, radiation cystitis, cyclophosphamide induced cystitis and severe infection complicating all of these. When irrigation of the bladder through a three-way catheter fail to stop the haematuria, a life-threatening situation can develop. Blood transfusion may not keep pace with the rate of blood loss. Patients with massive uncontrollable haematuria are often elderly and already extremely frail.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with locally advanced, metastatic bladder cancer or otherwise incurable with: Intractable bleeding	Palliative radiotherapy Palliative TURBT Urinary diversion Embolisation Palliative chemotherapy Tranexamic acid	Best supportive care Each other	• Successful treatment of bleeding • Requirement for transfusion • Patient-reported distress • Treatment-related mortality • Treatment related morbidity • Health-related quality of life, inc patient & carer reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (EH).

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

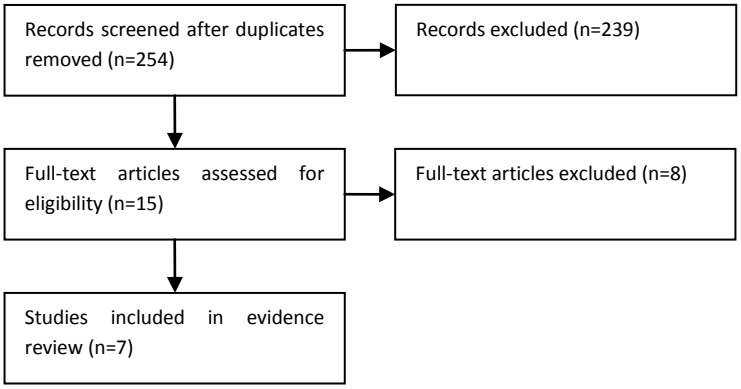
Data synthesis

Data from comparative studies were extracted into RevMan and risk ratios were calculated where possible. No meta-analysis was possible for this review.

RESULTS

Result of the literature searches

Figure 77. Study flow diagram



Study quality and results

Included studies are summarised in Tables 183-185.

Evidence statements

Palliative radiotherapy

One observational study (Srinivasan et al., 1994) provided very low quality evidence about the relative effectiveness of hypofractionated (two-fraction) radiotherapy and conventional palliative radiotherapy in 41 patients selected by performance status. 59% of those receiving two-fraction radiotherapy had clearance of haematuria compared to 16% of those receiving conventional palliation (RR 3.74, 95% CI 1.25 to 11.19). One observational study of 32 patients also selected for hypofractionated radiotherapy if they had a poor performance status (Lacarriere et al., 2013). After 2 weeks of radiotherapy, 79% of patients receiving hypofractionated radiotherapy (20Gy/5 fractions/1 week) and 54% of the conventional radiotherapy (30Gy/10 fractions/2 weeks) group had complete clearance of hematuria (RR 1.47, 95% CI 0.84 to 2.55). At six months 37% and 23% in the hypofractionated and conventional radiotherapy group had no haematuria (RR 1.60, 95% CI 0.5 to 5.06).

Embolisation

Four observational studies including a total of 67 patients provided very low quality evidence for embolisation of the internal iliac arteries. Immediate control of bleeding was seen in 57/67 (85%) patients, with control rates ranging from 82% to 100% across studies. Permanent control of bleeding with mean follow-up ranging from 10 to 22 months across studies was achieved in 34/66 (51.5%) patients. The range of permanent bleeding control rates ranged from 43% to 100% across studies. After embolisation, 27% of patients required transfusion for haematuria. None of the studies reported any major treatment-related complications, except for in Jenkins et al. (1996), where one patient who did not receive prophylactic antibiotics died from septic shock 12 hours after embolisation. Ligouri et al. (2010) reported that minor complications were post-embolisation syndrome (27%), fever (11%), gluteal pain (14%), and nausea (2%).

Chemotherapy

One observational study (Mantadakis et al., 2004) provided very low quality evidence of regional intra-arterial chemotherapy (RIAC) for the symptomatic relief of patients with advanced bladder cancer who were unsuitable for surgery. Gross haematuria was present in all 32 patients prior to RIAC, which had resolved in 24/32 (75%) after treatment. There were no hemorrhagic, thrombotic or embolic complications, and no episodes of nausea or emesis. One patient developed grade three mucositis.

Table 186. GRADE evidence profile: Hypofractionated radiotherapy versus conventional palliative radiotherapy for intractable bleeding

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypofractionated RT	Conventional RT	Relative (95% CI)	Absolute	
Clearance of haematuria											
1[1]	observational studies	none	none	none	serious[2]	none	13/22 (59.1%)	3/19 (15.8%)	RR 3.74 (1.25 to 11.19)	433 more per 1000 (from 39 more to 1000 more)	⊕OOO VERY LOW
Clearance or improvement of haematuria (assessed with: Stopped completely or haematuria but without hospitalisation)											
1[1]	observational studies	none	none	none	serious[2]	none	19/22 (86.4%)	13/19 (68.4%)	RR 1.26 (0.89 to 1.79)	178 more per 1000 (from 75 fewer to 541 more)	⊕OOO VERY LOW
Clearance of haematuria at 2 weeks (Common Terminology Criteria for Adverse Events)											
1[3]	observational studies	none	none	none	serious[2]	none	15/19 (78.9%)	7/13 (53.8%)	RR 1.47 (0.84 to 2.55)	253 more per 1000 (from 86 fewer to 835 more)	⊕OOO VERY LOW
Clearance of haematuria at 6 months (Common Terminology Criteria for Adverse Events)											
1[3]	observational studies	none	none	none	serious[2]	none	7/19 (36.8%)	3/13 (23.1%)	RR 1.60 (0.5 to 5.06)	138 more per 1000 (from 115 fewer to 937 more)	⊕OOO VERY LOW
Requirement for transfusion											
0	No evidence available										
Patient-reported distress											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Quality of life											
0	No evidence available										

[1] Srinivasan (1994); [2] Low number of events/small sample size limits precision; [3] Lacarriere (2013)

Table 187. GRADE evidence profile: Embolisation for intractable bleeding

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Embolisation**	**Control**	**Relative (95% CI)**	**Absolute**	
Initial control of bleeding											
4[1]	observational studies	none	none	none	serious[2]	none	57/67 (85.1%)	n/a	-	-	⊕OOO VERY LOW
Permanent control of bleeding (mean follow-up ranged from 10-22 months across studies)											
4[1]	observational studies	none	none	none	serious[2]	none	34/66 (51.5%)	n/a	-	-	⊕OOO VERY LOW
Requirement for transfusion (after treatment)											
4[1]	observational studies	none	none	none	serious[2]	none	18/67 (26.9%)	n/a	-	-	⊕OOO VERY LOW
Patient-reported distress											
0	No evidence available										
Treatment-related mortality											
4[1]	observational studies	none	none	none	serious[2]	none	1/67 (1.5%)[3]	n/a	-	-	⊕OOO VERY LOW
Treatment-related morbidity											
4[1]	observational studies	none	none	none	serious[2]	none	N=67[4]	n/a	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Ligouri 2010; El-Assmy 2007; Nabi 2003; Jenkins 1996; [2] Small sample size / low number of events limits precision; [3] One patient who did not receive prophylactic antibiotics died from septic shock 12 hours after embolisation (Jenkins, 1996); [4] All studies reported no major complications. Ligouri (2010) reported minor complications: post-embolisation syndrome 27%, fever 11%, gluteal pain 14%, nausea 2%. Jenkins (1996) reported that 3/10 patients developed moderate buttock and thigh pain lasting a maximum of 3 days.

Table 188. GRADE evidence profile: Regional intra-arterial chemotherapy (RIAC) for advanced bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RIAC	Control	Relative (95% CI)	Absolute	
Successful treatment of bleeding (resolution of gross haematuria)											
1[1]	observational studies	none	none	none	serious[2]	none	24/32 (75%)	n/a	-	-	⊕OOO VERY LOW
Requirement for transfusion											
0	No evidence available										
Patient-reported distress											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity (assessed with: hemorrhagic, thrombotic or embolic complications)											
1[1]	observational studies	none	none	none	serious[2]	none	0/32 (0%)	n/a	-	-	⊕OOO VERY LOW
Grade 3-4 adverse events											
1[1]	observational studies	none	none	none	serious[2]	none	1/32 (3.1%)	n/a	-	-	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Mantadakis 2004; [2] Small sample size / low number of events limits precision

References to included studies

El-Assmy, A and Mohsen, T. Internal iliac artery embolization for the control of severe bladder hemorrhage secondary to carcinoma: long-term follow-up. The scientific world journal 2007; 7: 1567-1574.

Jenkins, CNJ and McIvor, J. Survival after embolization of the internal iliac arteries in ten patients with severe haematuria due to recurrent pelvic carcinoma. Clinical Radiology 1996; 51(12): 865-868.

Lacarriere, E et al. The efficacy of hemostatic radiotherapy for bladder cancer-related hematuria in patients unfit for surgery. International Braz J Urol 2013; 39(6): 808-816.

Liguori, G et al. Intractable haematuria: long-term results after selective embolization of the internal iliac arteries. BJU International 2010; 106(4): 500-503.

Mantadakis, E et al. Symptomatic relief of patients with advanced bladder carcinoma after regional intra-arterial chemotherapy. Anticancer Research 2003; 23(6D): 5143-5147.

Nabi, G et al. Therapeutic transcatheter arterial embolization in the management of intractable haemorrhage from pelvic urological malignancies: preliminary experience and long-term follow-up. BJU International 2003; 92(3): 245-247.

Srinivasan, V, Brown, CH, and Turner, AG. A comparison of two radiotherapy regimens for the treatment of symptoms from advanced bladder cancer. Clinical Oncology 1994; 6(1): 11-13.

References to excluded studies (with reasons for exclusion)

Reason: case study

De Berardinis, E et al. Superselective embolization of bladder arteries in the treatment of intractable bladder haemorrhage. International Journal of Urology 2005; 12(5): 503-505.

Reason: not relevant to PICO

Zebic, N, Weinknecht, S, and Kroepfl, D. Radical cystectomy in patients aged > or = 75 years: an updated review of patients treated with curative and palliative intent. BJU International 2005; 95(9): 1211-1214.

Malgor, RD et al. Evolution from open surgical to endovascular treatment of ureteral-iliac artery fistula. Journal of Vascular Surgery 2012; 55(4): 1072-1080.

Sun, H. Transcatheter superselective arterial embolization for the treatment of massive hemorrhage due to malignant gestational trophoblastic tumors. Journal of Interventional Radiology 2010; 19(6): 447-450.

Reason: abstract only

Suvorova, YV and Tarazov, PG. Transcatheter embolization vs surgical ligation in the treatment of bleeding bladder neoplasms. European Journal of Cancer 1997; 33: 149-149.

Reason: expert review/not relevant to PICO

Abt, D et al. Therapeutic options for intractable hematuria in advanced bladder cancer. International Journal of Urology 2013; 20(7): 651-660.

Ghahestani, SM and Shakhssalim, N. Palliative treatment of intractable hematuria in context of advanced bladder cancer: a systematic review. [Review] [40 refs]. Urology Journal 2009; 6(3): 149-156.

Guven S., L. Intractable Bladder Hemorrhage: Providing a Treatment Algorithm for a Complex Clinical Problem. Current Bladder Dysfunction Reports 2011; 6(4): 258-264.

Evidence tables

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Additional comments
Srinivasan (1994) UK	Observational study (appears retrospective) 1982-1989	41 patients T3-4, Grade 2-3 TCC treated by palliative radiotherapy, presenting with haematuria and local pain	19 patients with reasonable PS (WHO grade ≤3) treated with conventional palliative treatment; 22 patients with poor performance status (WHO grade ≥4) accelerated radiotherapy. Mean age 78.4 years in 2-fraction group compared to 71.6 yrs in conventional group.	Conventional palliative treatment 4500cGy in 12 fractions over 26 days Both regimens used supervoltage photons. From 1984 volume was localised with CT.	Accelerated radiotherapy 1700cGy in 2 fractions over 3 days.	Not reported. Patients follow-up until death.	**Clearance of haematuria:** 59% (13/22) 2-fraction, 16% (3/19) conventional **Improvement of pain:** 73% (16/22) 2-fraction, 37% (7/19) conventional RT. Disease was fatal in all patients **Overall survival:** Mean 9.77 months 2-fraction vs 14.47 months conventional	No pain data for 7 patients. Time to symptom improvement not reported.
Ligouri 2010 Italy	Case series 1997-2009	44 patients with intractable haematuria secondary to advanced pelvic tumour arising from or invading the bladder.	<table><tr><td></td><td>N</td></tr><tr><td>Male</td><td>30</td></tr><tr><td>Female</td><td>14</td></tr><tr><td>Mean age</td><td>79 (51-95)</td></tr><tr><td></td><td></td></tr><tr><td>TCC bladder</td><td>24</td></tr><tr><td>prostate</td><td>12</td></tr><tr><td>uterus</td><td>5</td></tr><tr><td>vagina</td><td>1</td></tr><tr><td>rectum</td><td>2</td></tr><tr><td>kidney</td><td>3</td></tr><tr><td>Prostate and bladder</td><td>2</td></tr><tr><td>Prostate and kidney</td><td>1</td></tr><tr><td>Cystitis after RT</td><td>1</td></tr><tr><td></td><td></td></tr><tr><td>Cardiac history</td><td>20 (51)</td></tr><tr><td>Renal failure</td><td>10 (26)</td></tr><tr><td>Diabetes</td><td>7 (18)</td></tr><tr><td>cold</td><td>6 (15)</td></tr><tr><td>Hypertension</td><td>9 (23)</td></tr><tr><td>Peripheral vascular disease</td><td>5 (13)</td></tr><tr><td>Anaemia</td><td>7 (18)</td></tr></table>	Selective embolisation of internal iliac arteries. Simple measures to control bleeding by continuous irrigation using a 3-way catheter or cystodiathermy had been unsuccessful. All patients had complete coagulation profiles to exclude coagulopathy and perioperative antibiotic therapy. Used pre-curved Cobra or Simmons type 1 or 2 catheters and a hydrophilic guidewire. Artery embolised with unresorbable polyvinyl alcohol particles unless technically unfeasible. Sometimes to obtain more proximal occlusion, embolization was completed using	N/a	Mean 10.5 months (1-97)	**Initial complete control of bleeding:** 36/44 (82%) **Permanent control of bleeding:** at mean follow-up of 10.5 months 19/44 (43%). A second TAE session was required in 5 (11%) patients and it was successful in two of them. **Requirement for transfusion:** 24 (55%) required transfusion before TAE, 13 (30%) required more blood products after TAE **Complications:** No major complications over follow-up. Minor complications were post-embolization syndrome 12 (27%), fever (11%), gluteal pain (14%), nausea (2%), exterior	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Additional comments
				impermanent embolic agents.			genital oedema (5%).	
El-Assmy 2007 Egypt	Case series 1998-2005	7 patients with advanced bladder cancer and intractable bladder haemorrhage who were unsuitable for surgical treatment.	6 male, 1 female. Mean age 61 (55-68). 6 patients had TCC, 1 patient had squamous cell carcinoma. All had conservative treatment before transcatheter arterial embolisation (TAE), including continuous bladder irrigation using a 3-way catheter and attempts to control bleeding endoscopically. 2 had palliative RT to control bleeding	Embolization of bilateral iliac arteries. Selective catheterisation of the internal iliac artery. Angiography used to test the success of the procedure. Embolized using platinum mircocoils through 6F angiographic catheter. The procedure repeated on the opposite side using an ipsilateral or contralateral procedure.	n/a	Mean 10 months (6-12)	**Immediate control of bleeding:** 7/7/ (100%) after mean 4 days **Permanent control:** at mean 10 months follow-up 4/7 (57%). **Transfusion:** 3 patients developed haematuria and required 2.1 transfusion units **Complications:** no significant complications related to embolization	
Nabi 2003 UK	Case series 1997-2001	6 patients with advanced pelvic malignancy and intractable haemorrhage	3 advanced bladder TCC , 3 advanced adenocarcinoma of prostate. Mean age 80 years (70-87) All had conservative treatment before TAE, including continous bladder irrigation using a 3-way catheter and attempts to control bleeding endoscopically. 3 had palliative RT to control bleeding.	Bilateral internal iliac artery embolization. Iliac arteries were selectively catheterised using pre-curved catheters. Angiography used after embolization to ensure complete occlusion of blood flow. Embolized using tungsten/platinum coils, irrespective of whether bleeding was detected or not on angiographic study. The procedure repeated on the opposite side using an ipsilateral or contralateral procedure.	n/a	Mean 22 months (10-60)	**Immediate control of bleeding:** 5/6 (83%). 1 patient the bleeding was successfully embolised at a second attempt. **Permanent control of bleeding:** 6/6 (100%) at mean 22 months follow-up. **Transfusion:** no patient required transfusion after TAE or emergency admissions for control of haematuria. **Complications:** No major complications. Minor complications – nausea, fever and vomiting (n=3, 50%).	
Jenkins 1996	Case series	10 patients with life	Mean age 73 years (58-85). 7 bladder TCC, 1 carcinoma of cervix, 1	Bilateral internal iliac artery embolisation. Iliac	n/a	Patients followed	**Initial control of bleeding:** 9/10 (90%). In 5/9 patients	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Additional comments
UK	1979-1992	threatening haematuria secondary to inoperable pelvic carcinoma arising from or invading the bladder	rectum, 1 sigmoid colon.	arteries were catheterised and embolic material discharged into anterior divisions or the main stems of the internal iliac arteries if the interior divisions could not be easily catheterised or branched very close to their origins. Occlusion of vessels was assessed by repeated small injections of contrast.		until death.	surviving more than 24h there was complete control of haematuria lasting until patient's death. **Requirement for transfusion:** 2 patients required blood transfusion when haematuria recurred after 5 and 1.4 months. **Complications:** One patient died from septic shock. 3 patients developed mod buttock and thigh pain lasting max of 3 days. **Treatment related mortality:** 4 patients died within 2 wks. 1 patient who did not receive prophylactic antibiotics died of septic shock 12h later. 3 patients deaths attributed to tumour not haematuria.	
Mantadakis 2003 Greece	Prospective observational study	32 patients with advanced bladder carcinoma. Unfit for or refused surgery with adequate bone marrow and renal	30 male, 2 female. Median age 68 yrs (range 47-85). 14 T3N0M0, 10 T4N0M0, 4 T4N1M0, 4T4NxM0. 29 pure TCC. All patients had gross haematuria prior to RIAC. 7 had diversion of a dilated urinary tract prior to RIAC	Regional intra-arterial chemotherapy (RIAC). Epirubicin 10mg over 2 hrs on each internal iliac artery on the 1st – 3rd day of each chemo (total 60mg epirubicin per cycle). Systemic chemo i.v. leucovorin 200mg over 2hrs and 5FU 750mg per day on 1st through 3rd day	n/a	NR	**Control of bleeding:** 24/32 had resolution of gross haematuria. Persisted in 8 patients. **Treatment-related morbidity:** no hemorrhagic, thrombotic or embolic complications. One UTI, one acute tubular necrosis, one mild alopecia. No nausea or	

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Additional comments
		function. Distant mets excluded		of each cycle. Cycle repeated every 21 days. All patients completed chemo, median 4 cycles per patient (range 1-6).			emesis. 8 G1 leukopenia, 6 G1 mucositis, one G3 mucositis, 4 G1 diarrhea, 3 G1 thrombocytopenia.	
Lacarriere 2013 France	Retrospective observational study 1993-2009	32 bladder cancer patients unfit for surgery due to age or medical comorbidities	Patients with gross haematuria from bladder cancer, unfit for surgery, no previous pelvic radiotherapy. Coagulation disorders excluded. Mean age 81 (range 65-93)y. 20 male, 12 female. ECOG PS 2.5 (range 1-4). 22% Ta-T1, 38% T2, 19% T3, 22% T4, 91% G3 16 (50%) N+, 11 (34%) M+. Group A younger and lower PS and fewer comorbidities than Group B.	External radiotherapy using high energy photon therapy, with 4 orthogonal beams. Clinical target volume was the bladder. Lymph nodes not considered for treatment in palliative setting. Protocols dependant on general health of patient. Protocol A (n=13): 30Gy in 10 fractions over 2 weeks if ECOG PS ≤2.	Protocol B (n=19): Hypofractionated 20Gy in 5 fractions for 1 week if ECOG PS >2.	Mean 25mo (range 7-42)	CTC AE used to evaluate intensity of haematuria. 22 (69%) presented no haematuria after 2 weeks. 7 (54%) group A no haematuria vs. 15 (79%) Group B (p=0.139). Relapse defined as presence of gross haematuria during evaluation or need for other procedures to achieve hemostasis. After 6 months 69% of all patients had relapsed, with no difference in tumour subgroup or by ECOG PS.	40 patients enrolled, 8 excluded

5.2.4 Intractable pelvic pain

Review question: What specific interventions are most effective for patients with incurable bladder cancer and pelvic pain?

Rationale

Intractable pain is one of the most serious end-of-life complications for patients with bladder cancer because it is difficult to manage and it is frightening for the patient and their carers.

This review question will look primarily at medical interventions for the management of intractable pain but the location in which they are administered is also important to patients. Most patients do not want to die in hospital and would refer to die at home or in a hospice. A recent publication by the End of Life Care Intelligence Network showed that 51% of bladder cancer patients die in hospital compared with 46% for urological cancer patients as a whole.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with incurable cancer related pelvic pain excluding pain due to bone mets	Nerve block Palliative radiotherapy Chemotherapy for bladder cancer Specialist palliative care/Pain specialist	Best supportive care, inc opioids Each other	• Patient-reported pain • Treatment-related morbidity • Health-related quality of life, inc patient & carer reported outcomes

METHODS

Information sources

A literature search was performed by the information specialist (EH)

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO. The full articles were then obtained for potentially relevant studies and checked against the inclusion criteria.

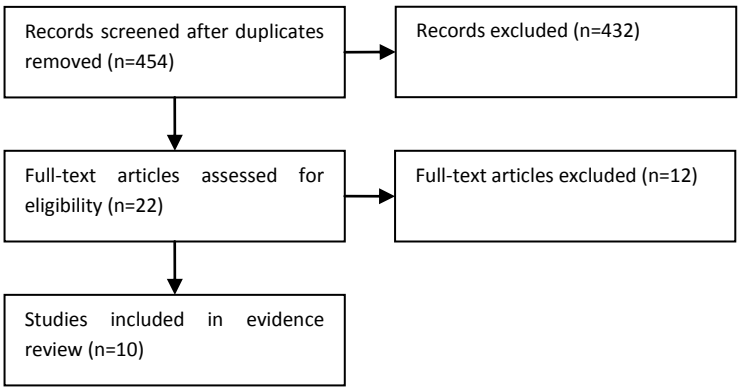
Data synthesis

Data from comparative studies were extracted into RevMan and risk ratios were calculated where possible. No meta-analysis was possible for this review.

RESULTS

Result of the literature searches

Figure 78. Study flow diagram



Study quality and results

All studies identified for this evidence review were non-comparative observational studies. The evidence is summarised in Tables 189-191.

Evidence statements

Radiotherapy

One observational study (Srinivasan et al., 1994) provided very low quality evidence about the relative effectiveness of hypofractionated (two-fraction) radiotherapy and conventional palliative radiotherapy in 41 patients selected by performance status. Pain improved in 73% of those treated with two-fraction radiotherapy compared to 37% of those treated with conventional palliation (RR 1.97, 95% CI 1.04 to 3.75). One study (58 patients) of hypofractionated radiotherapy and one study (12 patients) of short course accelerated 3D-CRT both reported a decrease in patient-reported pain after treatment, as measured on a visual analogue scale (VAS). These two studies reported an acute Grade 1-2 GI toxicity rate of 21% and an acute Grade 1-2 GU toxicity rate of 35% (Kouloulias et al., 2013; Caravatta et al., 2012). One study provided very low quality evidence for quality of life in 13 patients, reporting no statistically significant difference between baseline and post-treatment scores, although an improvement was noted in all indexes (Caravatta et al., 2012).

Chemotherapy

Very low quality evidence from one prospective nonrandomised phase II study (30 patients) of second-line gemcitabine chemotherapy in cisplatin-refractory patients, reported that VAS pain values significantly improved in the group of patients who responded to chemotherapy (Albers et al., 2002). One retrospective study of 35 patients receiving second-line gemcitabine and paclitaxel chemotherapy, reported very low quality evidence that 80% (28/35) of patients reported a decrease in VAS scores without increasing the dose of analgesics or had a decrease in analgesic consumption (Miyata et al., 2012). The most common toxicity reported in both studies was Grade 3-4 Leucopenia (36% with gemcitabine monotherapy, 14% with gemcitabine/paclitaxel). Very low quality evidence for quality of life as measured by the 10-point Spitzer scale was reported in one study (Albers et al., 2002). Mean quality of life scores for patients who did not respond to chemotherapy decreased before and after treatment (7.8 ±2.4 to 6.7 ±2.2), representing a worsening of quality of life. Quality of life scores for responders were similar before and after treatment (8.0 ±1.6 to 8.1 ±2.5).

Nerve block

Evidence of very low quality was provided by five studies reporting on the treatment of pelvic pain with a hypogastric plexus block. Two studies reported that satisfactory pain relief was achieved in 72% (133/185) of patients after one or two procedures, who all reported a VAS pain score of 8 or more out of 10 (worst possible pain) before the procedure (De Leon-Casasola et al., 1993; Plancarte et al., 1997). One study of 28 patients reported a mean pain reduction of 70% as assessed with verbal and visual analogue scales before and after treatment, although mean patient scores at baseline and follow-up were not reported (Plancarte et al., 1990). One study reported that VAS pain scores decreased from baseline at 24h, 1 week, 1 month and 2 months after treatment ($p<0.05$), but at three months mean scores increased and were no different from baseline (Gamal et al., 2006). Four studies (including 225 patients) provided very low quality evidence for treatment-related morbidity, with three studies reporting no intraoperative complications and one study (Gamal et al., 2006) reporting intravascular puncture (n=2, 13%) and urinary injury (n=4, 27%).

Table 189. GRADE evidence profile: Radiotherapy for cancer-related pelvic pain in patients with advanced cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypofractionated RT	Conventional RT	Relative (95% CI)	Absolute	
Relief or improvement in pain (assessed with: Opiates discontinued or at least a 50% reduction in opiate requirement)											
1[1]	observational studies	serious[2]	none	none	serious[3]	none	16/22 (72.7%)	7/19 (36.8%)	RR 1.97 (1.04 to 3.75)	357 more per 1000 (from 15 more to 1000 more)	⊕OOO VERY LOW
Patient-reported pain (assessed with: Mean (SD) Visual Analog Scale (VAS) score – scale 0 (no pain) to 10 (most pain))											
1[4]	observational studies	none	none	none	serious[3]	none	N=58	n/a	-	4.2 ±1.1 before RT and 1.8 ±0.6 after RT (no *p* value)	⊕OOO VERY LOW
Patient-reported pain (assessed with: Mean (SD) Visual Analog Scale (VAS) score – scale 0 (no pain) to 10 (most pain))											
1[5]	observational studies	none	none	none	serious[3]	none	N=12	n/a	-	6 ±2 before RT and 3 ±2.3 after RT (*p*=.0002)	⊕OOO VERY LOW
Treatment-related morbidity (assessed with: acute Grade 1-2 GI toxicity; follow-up 3-6 months)											
2[4,5]	observational studies	none	none	none	serious[3]	none	18/85 (21.2%)	n/a	-	-	⊕OOO VERY LOW
Treatment-related morbidity (assessed with: acute Grade 1-2 GU toxicity; follow-up 3-6 months)											
2[4,5]	observational studies	none	none	none	serious[3]	none	30/85 (35.3%)	n/a	-	-	⊕OOO VERY LOW
Health-related quality of life (assessed with: Cancer Linear Analog Scale, measured well-being, fatigue, and ability to perform daily activities)											
1[5]	observational studies	serious[6]	none	none	serious[3]	none	N=13	n/a		No significant difference from baseline to post-treatment	⊕OOO VERY LOW

[1] Srinivasan (1994); [2] Patients selected for treatments based on performance status. Hypofractionated group were older and with poor performance status (WHO grade 4 or more). No pain data for 7 patients; [3] Low number of events/small sample size limits precision; [4] Kouloulias (2013); [5] Caravatta (2012) short course accelerated 3D-CRT; [6] Unclear if patients completing the QoL measure had received RT for pain management.

Table 190. GRADE evidence profile: Chemotherapy for cancer-related pelvic pain in patients with advanced cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy	Control	Relative (95% CI)	Absolute	
Patient-reported pain (non-responders to chemotherapy) (follow-up mean 8.4 months; measured with: Visual Analog Scale (7-point scale); Better indicated by higher values)											
1[1]	observational studies	none	none	none	serious[2]	none	15	-	-	5.3±1.8 before and 4.8±1.5 after CT (increase in pain, no *p* value)	⊕OOO VERY LOW
Patient-reported pain (responders to chemotherapy) (follow-up mean 8.4 months; measured with: Visual Analog Scale (7-point scale); Better indicated by higher values)											
1[1]	observational studies	none	none	none	serious[2]	none	13	-	-	4.3±1.9 before and 5.8 ±1.3 after CT (decrease in pain, $p<0.05$)	⊕OOO VERY LOW
Patient-reported pain (follow-up median 10 months; assessed with: Improved pain score on VAS)											
1[3]	observational studies	none	none	none	serious[2]	none	24/35 (68.6%)	-	-	-	⊕OOO VERY LOW
Decrease in analgesic consumption (follow-up median 10 months)											
1[3]	observational studies	none	none	none	serious[2]	none	12/35 (34.3%)	-	-	-	⊕OOO VERY LOW
Decrease in analgesic consumption or decrease in VAS score without increasing analgesic dose (follow-up median 10 months)											
1[3]	observational studies	none	none	none	serious[2]	none	28/35 (80%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia (Gem)											
1[1]	observational studies	none	none	none	serious[2]	none	10/28 (35.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Leucopenia (Gem/Pac)											
1[3]	observational studies	none	none	none	serious[2]	none	5/35 (14.3%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (Gem)											
1[1]	observational studies	none	none	none	serious[2]	none	3/28 (10.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Thrombocytopenia (Gem/Pac)											
1[3]	observational studies	none	none	none	serious[2]	none	2/35 (5.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (Gem)											
1[1]	observational studies	none	none	none	serious[2]	none	3/28 (10.7%)	-	-	-	⊕OOO VERY LOW
Grade 3-4 Anaemia (Gem/Pac)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy	Control	Relative (95% CI)	Absolute	
1[2]	observational studies	none	none	none	serious[2]	none	2/35 (5.7%)	-	-	-	⊕OOO VERY LOW
Health-related quality of life (Responders to chemotherapy) (measured with: Spitzer index 10-point scale; Better indicated by higher values)											
1[1]	observational studies	none	none	none	serious[2]	none	13	-	-	8.0 ±1.6 before and 8.1 ±2.5 after CT (no *p* value)	⊕OOO VERY LOW
Health-related quality of life (Non-responders to chemotherapy) (measured with: Spitzer index 10-point scale; Better indicated by higher values)											
1[1]	observational studies	none	none	none	serious[2]	none	15	-	-	7.8 ±2.4 before and 6.7 ±2.2 after CT (no *p* value)	⊕OOO VERY LOW

[1] Albers 2002 (2nd line Gemcitabine); [2] Small sample size / low number of events limits precision; [3] Miyata 2012 (2nd line Gemcitabine/Paclitaxel)

Table 191. GRADE evidence profile: Hypogastric plexus block for cancer-related pelvic pain in patients with advanced cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypogastric plexus block	Control	Relative (95% CI)	Absolute	
Patient-reported pain (assessed with: Satisfactory pain relief after 1 or 2 procedures (all patients VAS score >8/10 (worst possible pain) before treatment)											
2[1]	observational studies	serious[2]	none	serious[3]	serious[4]	none	133/185 (71.9%)	n/a	-	-	⊕OOO VERY LOW
Patient-reported pain (assessed with: Visual and verbal analogue scale)											
1[5]	observational studies	serious[6]	none	serious[3]	serious[4]	none	N=28	n/a	-	mean reduction in pain =70%	⊕OOO VERY LOW
Patient-reported pain (assessed with: VAS score (scale 0 (no pain) to 10 (worst pain))											
1[7]	observational studies	serious[6]	none	serious[3]	serious[4]	none	N=30	n/a	-	see footnote[8]	⊕OOO VERY LOW
Patient-reported pain (assessed with: moderate or complete pain relief (4-grade subjective analogue scale - none, mild, moderate, complete))											
1[9]	observational studies	none	none	serious[10]	serious[4]	none	6/10 (60%)	n/a	-	-	⊕OOO VERY LOW
Treatment-related morbidity											
4[1,7,9]	observational studies	none	none	serious[3]	serious[4]	none	6/225 (2.7%)	n/a	-	see footnote[11]	⊕OOO VERY LOW
Health-related quality of life											
0	No evidence available										

[1] De Leon-Casasola 1993; Plancarte 1997; [2] In Plancarte (1997) only patients who had a positive response to diagnostic block received the neurolytic block; [3] Studies include mostly women with gynaecological cancers; [4] Low number of events / small sample size limits precision; [5] Plancarte 1990; [6] Poorly reported outcomes and method of outcome assessment. Mean scores not provided. [7] Gamal 2006; [8] Scores decreased from baseline at 24h, 1 week, 1 month and 2 months after block ($p<0.05$). At 3 months there was no difference from baseline; [9] Cariati 2002; [10] Mostly colorectal and uterine cancer patients; [11] All studies except for Gamal 2006 reported no intraoperative or long-term complications. Gamal reported Intravascular puncture (n=2, 13%), urinary injury (n=4, 27%)

References to included studies

Albers, P et al. Gemcitabine monotherapy as second-line treatment in cisplatin-refractory transitional cell carcinoma - prognostic factors for response and improvement of quality of life. Onkologie 2002; 25(1): 47-52.

Caravatta, L et al. Short-course accelerated radiotherapy in palliative treatment of advanced pelvic malignancies: a phase I study. International Journal of Radiation Oncology, Biology, Physics 2012; 83(5): e627-e631.

Cariati, M. CT-guided superior hypogastric plexus block. Journal of Computer Assisted Tomography 2002; 26(3): 428-431.

De Leon-Casasola, OA. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Pain 1993; Vol.54(2): 145-151.

Gamal, G, Helaly, M, and Labib, YM. Superior hypogastric block: transdiscal versus classic posterior approach in pelvic cancer pain. The.Clinical.journal of pain 2006; 22(6): 544-547.

Kouloulias, V et al. Evaluation of acute toxicity and symptoms palliation in a hypofractionated weekly schedule of external radiotherapy for elderly patients with muscular invasive bladder cancer. International Braz J Urol 2013; 39(1): 77-82.

Miyata, Y et al. Use of low-dose combined therapy with gemcitabine and paclitaxel for advanced urothelial cancer patients with resistance to cisplatin-containing therapy: a retrospective analysis. Cancer Chemotherapy & Pharmacology 2012; 70(3): 451-459.

Plancarte, R. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Regional Anesthesia 1997; 22(6): 562-568.

Plancarte, R. Superior hypogastric plexus block for pelvic cancer pain. Anesthesiology 1990; 73(2): 236-239.

Srinivasan, V, Brown, CH, and Turner, AG. A comparison of two radiotherapy regimens for the treatment of symptoms from advanced bladder cancer. Clinical Oncology (Royal College of Radiologists) 1994; 6(1): 11-13.

References to excluded studies (with reasons for exclusion)

Mantadakis, E et al. Symptomatic relief of patients with advanced bladder carcinoma after regional intra-arterial chemotherapy. Anticancer Research 2003; 23(6D): 5143-5147.

Reason: outcomes not relevant to PICO

Bosscher, H. Blockade of the superior hypogastric plexus block for visceral pelvic pain. Pain Practice 2001; 1(2): 162-170.

Reason: expert review

Fitzpatrick, JM et al. Treatment Decisions for Advanced Genitourinary Cancers: From Symptoms to Risk Assessment. European Urology Supplements 2009; 8(9): 738-746.

Reason: expert review

Ok, JH, Meyers, FJ, and Evans, CP. Medical and surgical palliative care of patients with urological malignancies. [Review] [48 refs]. Journal of Urology 2005; 174(4 Pt 1): 1177-1182.

Reason: expert review

Spagnoletti, G. Palliative radiotherapy for bladder cancer: A small retrospective study. Anticancer Research 2010; Conference(var.pagings): 4

Reason: abstract only

Pectasides, D et al. Combination chemotherapy with gemcitabine and ifosfamide as second-line treatment in metastatic urothelial cancer. A phase II trial conducted by the Hellenic Cooperative Oncology Group. Annals of Oncology 2001; 12(10): 1417-1422.

Reason: outcomes not relevant to PICO

Sarhan, TM. Male sexual dyfunction after unilateral and bilateral hypogastric plexus block for management of chronic cancer pelvic pain. European Journal of Pain Supplements 2011; Conference(var.pagings): 1

Reason: abstract only

Zygogianni, A et al. A weekly hypofractionated radiotherapeutic schedule for bladder carcinoma in elderly patients: local response, acute and late toxicity, dosimetric parameters and pain relief. Journal of B.U.On. 2013; 18(2): 407-412.

Reason: population not relevant to PICO (not pelvic pain)

Patt, RB. Superior hypogastric plexus block for neoplastic pelvic pain. Pain Management 1990; 3(5): 259-261.

Reason: review of Plancarte (1990)

Uchibayashi, T et al. Combined treatment of radiofrequency capacitive hyperthermia for urological malignancies. Oncology Reports 1994; 1(5): 937-940.

Reason: intervention not relevant to PICO

Baheti, DK. Neurolytic coeliac plexus block for upper abdominal malignancies: Review of 50 cases. Pain Clinic 1997; 10(1): 47-49.

Reason: population/intervention not relevant to PICO

Bajaj, P. Superior hypogastric plexus block for pelvic cancer pain. Journal of Anaesthesiology Clinical Pharmacology 2003; 19(2): 161-164.

Reason: majority of article is a copy of Plancarte 1990, highly unreliable paper

Evidence tables

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Additional comments
Srinivasan (1994) UK	Observational study (appears retrospective) 1982-1989	41 patients T3-4, Grade 2-3 TCC treated by palliative radiotherapy, presenting with haematuria and local pain	19 patients with reasonable PS (WHO grade ≤3) treated with conventional palliative treatment; 22 patients with poor performance status (WHO grade ≥4) accelerated radiotherapy. Mean age 78.4 years in 2-fraction group compared to 71.6 yrs in conventional group.	Conventional palliative treatment 4500cGy in 12 fractions over 26 days Both regimens used supervoltage photons. From 1984 volume was localised with CT.	Accelerated radiotherapy 1700cGy in 2 fractions over 3 days.	Not reported	**Improvement of pain:** 73% (16/22) 2-fraction, 37% (7/19) conventional RT. Disease was fatal in all patients **Overall survival:** Mean 9.77 months 2-fraction vs 14.47 months conventional	No pain data for 7 patients
Kouloulias 2013 Greece	Prospective observational study 2005-2011	58 patients with organ-confined (cT1-2, N0) bladder cancer. All inoperable, with poor PS, >75yrs. Excluded previous pelvic RT or cystectomy, LN mets, distant mets or hip prosthesis.	Median age: 77 (70-91) T1: 12 T2: 46 PS 60-70%: 10 PS 50-60%: 48 Male/female: 47/11	Hypofractionated 3DCRT-virtual CT planning used. Clinical target volume (the bladder) and planning target volume obtained by expanding CTV with a margin of 1cm in each direction and of 0.5cm posteriorly. Entire bladder was treated using 4-field technique with 15 MV x-ray energy beams. 36Gy in 6 weekly fractions.	N/a	3 months after RT treatment	**Acute Grade 1-2 GI toxicity:** 13/58 (22%) **Acute Grade 1-2 GU toxicity:** 19/58 (33%) No grade 3 or higher GI or GU toxicity. **Patient-reported pain:** VAS score improved from 4.2 (±1.1) to 1.8 (±0.6) (p<0.001).	
Caravatta 2012 Italy	Prospective observational study	27 patients with locally advanced cancer and metastatic disease, ECOG PS ≤3, no previous RT to same region.	Median age: 72 (47-86) Male: 11 (41) Female: 16 (59) ECOG PS 0: 7 (26) PS 1: 6 (22) PS 2: 9 (33.5) PS 3: 5 (18.5) Primary cancer site Gynaecologic: 48% Colorectal: 18.5%	Short course accelerated 3D conformal RT. CT planning used. Clinical target volume defined as primary tumour or metastatic site plus 1 cm margin. 1 cm margin in all directions added for planning target volume.	n/a	Median 6 months (range 3-28)	**Acute Grade 1-2 GI toxicity:** 5/27 **Acute Grade 1-2 GU toxicity:** 11/27 **Patient-reported pain:** 12 patients treated for pain control. Mean VAS score improved from 6 (±2) to 3 (±2.3) p=0.0002. 5 patients	Not all bladder cancer patients

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Additional comments
		12 patients received RT for pain control.	Genitourinary 33.5%	Patients received 14Gy (3.5Gy frations), 16Gy (4-Gy fractions), or 18 Gy (4.5Gy fractions) in 3 dose levels. Patients underwent RT on 2 consecutive days with twice-daily fractionation, with an interval of ≥8 hrs between fractions.			(41.7%) had complete pain relief, 6 patients (50%) showed more than 30% VAS reduction. 8 (66%) reported a reduction in pain score and 9 (75%) reported a reduced drug score. 1 of 4 patients discontinued opioid analgesic therapy. **Quality of life (Cancer Linear Analog Scales):** well-being, fatigue, ability to perform daily activities. 13 patients completed QOL VAS ranking. No significant differences between baseline and post-treatment, though improvement in all indexes was noted.	
Albers 2002 Germany	Prospective non-comparative phase 2 study 1998-1999	N=30, proven, measurable recurrent or progressing TCC, prior cisplatin-based chemo. No prior gemcitabine, chemo or RT within 4 weeks prior to study, no karnofsky PS <40, adequate liver and renal function.	86% prior radical surgery with adjuvant MVAC/MVEC or CM, 7% cystectomy with neoadjuvant MEC, 7% primary MVEC/MVAC without radical surgery 40% regional lymph node and distant metastases, 26% regional lymph nodes only, 26% distant mets only 28 patients evaluable for response and toxicity,	Gemcitabine 1250mg/m2 on day 1 & 8 of a 21-day course i.v. 30 mins. Maximum 6 courses (18 weeks) 9/28 completed 6 courses of treatment, 15 did not receive maximum number due to progression, 4 dropped out due to toxicity or personal reasons	n/a	Mean 8.4 months (0-25.3)	**Toxicity:** 36% (10/28) Grade 3-4 Leukocytopenia, 11% (3/28) thrombocytopenia, 11% (3/28) anemia, 11% (3/28) Grade 3 vomiting, 11% pulmonal toxicity, 3% (1/28) exanthema. 1 Grade 4 vomiting. **Quality of life (Spitzer index values 10-point scale):** In non-responders decreased from 7.8 ±2.4 to 6.7±2.2 at the end of treatment. In responders there was no change during treatment 8.0 ±1.6 before, 8.1 ±2.5 after. **Pain scale (7-point scale):** Non-responders showed decrease in pain values 5.3±1.8 to 4.8±1.5 (an increase in pain). Responders showed	QoL Spitzer questionnaire designed and validated for palliative care populations.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Additional comments
							improvement in pain from 4.3±1.9 to 5.8 ±1.3 (p<0.05)	
Miyata 2012 Japan	Retrospective observational study 2003-2011	35 patients with metastatic and/or recurrent UC previously treated with cisplatin containing chemo	<table><tr><td></td><td></td></tr><tr><td>Median age</td><td>68</td></tr><tr><td>Male</td><td>26 (74%)</td></tr><tr><td>Female</td><td>9 (25.7%)</td></tr><tr><td>PS0</td><td>14 (40)</td></tr><tr><td>PS1</td><td>16 (46)</td></tr><tr><td>PS2</td><td>5 (14)</td></tr><tr><td>Primary tumour site</td><td></td></tr><tr><td>UUT</td><td>13 (37)</td></tr><tr><td>Bladder</td><td>21 (60)</td></tr><tr><td>both</td><td>1 (2.9)</td></tr><tr><td>Prior treatment</td><td></td></tr><tr><td>Chemo</td><td>8 (23)</td></tr><tr><td>Chem+surgery</td><td>17 (49)</td></tr><tr><td>Chem+Rad</td><td>6 (17)</td></tr><tr><td>ChemRad+ surgery</td><td>4 (11)</td></tr><tr><td>2nd line CT</td><td>31 (89)</td></tr></table>	All patients progressed after cisplatin based therapy. Low dose GP: Gem 700mg/m^2 i.v. for 30mins on day 1 and 8 of each 28 day cycle. Pac at 70mg/m^2 i.v. over 3h on day 1 and 8 of each 28-day cycle. Dexamthasone sodium phosphate (6.6mg), diphenhydramine hydrochloride (50mg) and ranitidine hydrochloride (100mg) were administered before treatment. Median 5 treatment cycles per patient.	n/a	Median 10 months (IQR 4-19)	**Pain relief (VAS scale):** Median abdominal/back pain median VAS score 4 (3-6) and all needed analgesics. After CT scores were 2 (1-3) (p<0.001). Improved pain scores (n=24, 69%), decrease in analgesic consumption (n=12, 34%). Decrease in analgesic consumption or decrease in VAS score without increasing analgesic dose 28/35 (80%). **Toxicity:** Grade 3-4 anemia (n=2, 6%), leukopenia (n=5, 14%), thrombocytopenia (n=2, 6%). Grade 3-4 Fatigue 0, nausea/vomiting (n=1, 3%), neuropathy 0, skin rash (n=1, 2.9%).	
De Leon-Casasola 1993 USA	Observational study (appears prospective)	26 patients with pelvic pain from colorectal or gynaecological cancers that was no longer controlled with opioids or excessive sedation or side-effects from opioids. Excluded allergies to phenol, life expectancy <1	<table><tr><td>Mean age</td><td>55±8 years</td></tr><tr><td>Gynae cancer</td><td>22 (77%)</td></tr><tr><td>Prostate cancer</td><td>4 (15%)</td></tr><tr><td>Colorectal</td><td>2 (7%)</td></tr></table>	Hypogastric plexus block: Contrast medium used to determine accurate placement of needles. All underwent diagnostic block with 8ml 0.25% BUP injected through each needle. If 70% reduction in pain intensity a neurolytic block performed on following day. For neurolysis 8ml of 10% phenol (dissolved in sterile water) was used on each side. Criteria for success of	n/a	NR	**Pain relief (Visual Analog Pain Scale 0-10):** All patients 10/10 (worst pain) before block despite oral opioid therapy. Morphine sulphate mean was 953±722 mg/day before block to 420±354 2wks after block (p<0.0001). Patients in the success group were using sig less daily oral MS than patients in failure group (736±633 versus 1443 ±703 mg/day, p=0.02). % reduction in usage = 67% in success group and 45% in failure group. Overall 18 (69%) had satisfactory pain relief after 1	No bladder cancer patients. Length of follow-up not reported.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Additional comments
		mo, patients receiving RT/CT		block: 1)decrease in VAPS of at least 70% or pain intensity of less than 3 to 10 during first two weeks after neurolytic block. 2)decrease in opioid requirements of at least 30% resulting in disappearance of bothersome side-effects 2 wks after block. Patients with failed blocks after 2 consecutive attempts received continuous epidural BUP morphine.			or 2 procedures with a VAPS of ≤3. **Complications;** No intraoperative complications. No long-term complications.	
Gamal 2006 Egypt	Prospective observational study	30 patients with pelvic pain due to cancer and had been treated with analgesic medication according to WHO guidelines and still had pain on VAS >4 (0-10, worst pain)	<table><tr><td></td><td></td></tr><tr><td>Male</td><td>14 (47%)</td></tr><tr><td>female</td><td>16 (53%)</td></tr><tr><td>Mean age</td><td>59</td></tr><tr><td>Pain duration (mo)</td><td>5.4-6.1</td></tr><tr><td>Primary cancer site</td><td></td></tr><tr><td>Rectum</td><td>5 (16%)</td></tr><tr><td>Cervix</td><td>8 (27%)</td></tr><tr><td>Bladder</td><td>9 (30%)</td></tr><tr><td>endometrial</td><td>8 (27%)</td></tr></table>Patients with no contraindications to regional blockade and sympathetic blockade.	Superior hypogastric block: patients randomised into two groups - transdiscal approach (n=15) or block via classic posterior approach (n=15).	Transdiscal versus posterior approach	3 months	**VAS pain scores:** Scores decreased from baseline at 24h, 1 week, 1 month and 2 months after block ($p<0.05$). At 3 months there was no difference from baseline. No differences between the two groups at any timepoint. Daily morphine consumption decreased in both groups from baseline up to 2 months after block. No differences between 3 month and baseline. **Complications:** In the classic group: Intravascular puncture (n=2, 13%), urinary injury (n=4, 27%)	No details about randomisation to two groups.
Plancarte 1997 Mexico/USA	Prospective observational study	227 patients with pelvis pain and gynaecological, colorectal or	Excluded patients with anticoagulopathies, allergies to phenol, life expectancy <3 months, concurrent rad/CT or scheduled to receive treatment within 4 wks of	Superior hypogastric plexus block: L4-L5 intervertebral space was found and marked. Patient sedated. Accurate placement of	n/a	6 months	**Patient-reported pain:** Preblock VAS score 8-10 (n=159, 100%). No patients had score 8-10 post-block. Postblock VAS score 4-7 (n=60,	Oral morphine therapy not available in Mexico when

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Additional comments
		genitourinary cancer who had poor pain control – failed opioid therapy or excessive side-effects/sedation.	block, purely somatic and/or neuropathic pain. 159 (79%) had a positive response to diagnostic block and therefore available for neurolytic block. Mean age =48 years. 89% were women with gynaecological cancers, 17 males with prostate, colorectal or bladder carcinoma.	needles determined by collection of contrast medium just anterior to the L5-S1 intervertebral space. All patients had diagnostic block with 8ml of 0.25% bupivacaine injected through each needle. If patient reported a 50% reduction in pain intensity for 4 hrs, a neurolytic block was done on the following day. If patients failed to derive a benefit from this technique they were removed from study and offered epidural analgesia. For neurolysis 8ml of 10% phenol used on each side, dissolved in sterile water.			38%), score <4 (n=99, 62%). Overall 115/159 (72%) who responded to diagnostic block had satisfactory pain relief after one or two procedures. This is 51% (115/227) overall response for eligible patients **Complications:** No intraoperative complications, no long-term complications.	study was done. Mostly gynaecological cancers.
Plancarte 1990 USA/Mexico	Prospective observational study	28 patients – 22 female , 5 male	Mean age 36 years. All had chronic lower abdominal pain with a prominent visceral component, secondary to advanced cancer. (20 cervix, 4 prostate, 1 testicle, 1 post-radiation cystitis) Persistent pain despite radiotherapy, chemotherapy, non-opioid and opioid analgesics, and behavioural pain management.	Superior hypogastric plexus block: Location of L4-l5 interspace was located. Block used for either diagnostic/prognostic or therapeutic purposes. For diagnosis 6-8ml 0.25% bupivacaine was used. For therapeutic (neurolytic) blocks a total of 6-8ml 50% alcohol through each needle	n/a	Monthly until death	Visual and verbal analogue scales used to measure pain immediately before block and after at 30 mins, 1,2,4,5 and 24 hr, then monthly until death. **Patient-reported pain:** Mean reduction in pain of 70% was observed, residual pain seemed generally of somatic origin. Injections of epidural steroids, serial injections of 2-3% epidural phenol and or non-opioid analgesics used to control remaining somatic pain resulting in a global reduction of pain scores by 90%. No	Outcomes poorly reported. No mean scores. No bladder cancer patients.

Study, country	Study type, study period	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Additional comments
							return of pain in all but two patients.	
Cariati 2002 Italy	Observational study (appears prospective) 1995-2000	10 patients with pelvic malignancy and chronic severe pain which could be controlled only with high doses of NSAIDs	4 rectum/sigmoid adenocarcinoma, 3 uterine carcinoma, 2 bladder cancer, 1 secondary lesion of the right hip from laryngeal carcinoma. Nine treated with morphine sulphate, one with high levels of NSAIDs	CT-guided superior hypogastric neurolytic block with alcohol, using a single needle and anterior approach. All patients sedated before procedure. The first four patients had an injection of 10ml alcohol, 2 had 15ml and the last 4 patients had 20ml alcohol.	n/a	Not reported	**Complications:** No local complications such as hematomas, or puncture of vascular stricture. **Pain:** evaluated using a 4-grade subjective analogue scale (none, mild, moderate, complete). 4/10 Complete disappearance of pain lasting until patient death (60-160 days after procedure) and with no analgesics, 2/10 moderate reduction with no opioids, 3/10 mild reduction of pain (one died at 20 days, 2 had opioids restarted at 17 and 25 days). One patient had no benefit and restarted opioid treatment.	Mostly colorectal or uterine cancer.

Appendix 1 Review Protocols

Key clinical issue: What are the information and support needs of patients with bladder cancer, for instance at the point of diagnosis, those considering options for treatment, and those considering palliative care?

Rationale:
There are many differences in the experiences of bladder cancer patients and their families in relation to the information and support received during diagnosis, treatment, and into end of life care.

Poor communication has a great impact on the patient experience and is often the basis of hospital complaints. It is therefore vital that the information needs of bladder cancer patients are understood so that healthcare professionals can improve the processes involved. Communication with primary care teams is often poor and not timely and therefore improving this will improve the support of patients by having primary care teams fully up to date with a patients care pathway (e.g. making sure that the gateway between the GP and hospital care is smooth).

As has been the case with a succession of Governments, the current Coalition Government has made an explicit commitment to making "patient-centred" care a central principle in their plans for developing the NHS. The principle of 'patient-centredness' has been enshrined and embedded in one of the 7 Key Principles of the NHS Constitution.

There is a body of research which supports the efficacy of the approach in enhancing outcomes for patients with respect to their psychological, emotional and social wellbeing. It is now become a requirement (and clear expectation) that all cancer patients should have a Holistic Needs Assessment at key stages of their pathway.

There is also a developing body of research which suggests that an improved patient experience with better information, communication (including correspondence, scheduling of procedures, appointment systems, etc.) and support, as well as greater involvement for patients (and their carers) in decision making and in exercising choice throughout their treatment (as well as in the self-management of their own ongoing care) can have a positive and measurably beneficial effect on clinical outcomes.

There are many examples of excellent and pioneering work being undertaken across the NHS (including work around Information Prescriptions, Survivorship, Holistic Needs Assessments, Distress Thermometers, Self-Care and Self-Management, etc.). NICE has now also established a set of Quality Standards within its Clinical Guidance on the Patient Experience. However, there remains significant variation in performance and standards in day to day practice - between Trusts/hospitals and cancer groups. This continues to be reflected in both the National Patient Experience Surveys and National Cancer Peer Reviews.

Within the National Patient Experience Survey there appears to be a significant qualitative/quantitative difference in the reported patient experience between Prostrate Cancer patients and Urological Cancer (including Bladder Cancer) patient groups. However, both sets of patients are treated within the same generic Urological Services. This strongly suggests an identified need for further specific research into patient reported outcomes of bladder cancer patients. All the evidence and completed research points to the significant contribution of the clinical nurse specialist (CNS) or key worker input in the provision of information and support to cancer patients and the resultant reported level of patient satisfaction. It is important to identify which elements of

information and support provided by CNS's and palliative care specialists are most important to bladder cancer patients.

Clincal question: What are the causative and contributory factors that result in the comparatively low levels of reported patient satisfaction (c.f. the National Patient Satisfaction Surveys) for bladder cancer patients within the group of urological cancers?

This question will be answered by reviewing the National Cancer Patient Experience Survey 2011/12 – National Report, published by the Department of Health. The surveys are designed to monitor national progress on improving outcomes in cancer patient experience. The survey covers the patient pathway from seeing their GP, to diagnosis, treatment and outpatient care. Areas in the survey which had less positive assessments by cancer patients will be reported. Also, areas which urological cancers patients (excluding prostate cancer) rated lower than other cancer groups will be reviewed, which will provide some indication as to the overall comparatively lower levels of patient satisfaction within the urological cancers group (which includes bladder cancer patients). Data will also be gathered from the PROMS bladder cancer quality of life survey, if the results of the survey are available before guideline is published.

Clinical question: Which elements of the information and support provided by clinical nurse specialists (CNS)/key workers are most important for bladder cancer patients and/or their carers, at the various stages of the patient pathway?

Sample	Phenomenon of interest	Evaluation
Patients with bladder cancer & their carers	Information & support provided by a clinical nurse specialist or key worker	Patient and/or carer satisfaction (with communication, information support and treatment received) Health-related quality of life (inc. patient and carer-reported outcomes) Understanding/knowledge of disease and treatment Psychological factors (e.g. distress, coping) Perceived social support Informed choice and decision-making Ability to self-manage condition/side-effects Referral to support groups/networks

Consider:
Gender/age/ethnicity/socioeconomic status/location/disability
Stage/grade of disease
Timing and duration of referral to specialist nurse (e.g. at diagnosis, during treatment)
Perceived quality of care received from nurse specialist
Amount and quality of information and support provided (e.g. emotional, financial, physical, social, psychological)
Patients perceived ability and confidence in making informed choices about treatment etc

Clinical question section 2.3: Which elements of specialist palliative care services are most important for bladder cancer patients and/or their carers during end-of-life care?

Sample	Phenomenon of interest	Evaluation
Patients with bladder cancer (& their carers) who are candidates for palliative care	Palliative care specialists during end-of-life care	Patient (and carer) satisfaction (with communication, information, support and treatment received) Health-related quality of life (inc. patient and carer-reported outcomes) Understanding/knowledge of disease and treatment Psychological factors (e.g. distress, coping) Perceived social support Informed choice and decision-making Ability to self-manage condition/side-effects Referral to support groups/networks

Consider:
Gender/age/ethnicity/socioeconomic status/location/disability
Timing and duration of referral to palliative care specialist
Perceived quality of care received
Amount and quality of information and support provided (e.g. emotional, financial, physical, social, psychological)

Why are the outcomes listed in the above PICO important to patients?
For bladder cancer patients (as with all other patients) – successful interventions and positive clinical outcomes are, obviously, paramount. How these outcomes are actually delivered is of equal importance in terms of overall wellbeing. There is a growing body of research evidence now that indicates that a 'happy', well informed and properly supported patient who is helped to feel included in decisions and choices about their care + treatment – is more likely to have positive clinical outcomes.
Regrettably, not all bladder cancer patients will survive and how you are treated along your treatment journey may be the outcome that matters most.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No date limit will be applied to the search
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No study design filters will be used as evidence will come from qualitative studies, survey data or case series studies.
List useful search terms.	Bladder Cancer diagnosis and/or treatment,

	Patient Reported Outcomes, Patient Experience, Patient Satisfaction, health related wellbeing, psychosocial outcomes, psychological and/or emotional wellbeing, preferences and choices, decision making and self-management – all of the above especially if they relate specifically to bladder cancer

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	We will extract qualitative and quantitative data depending on what studies are found from the search. The data will be presented according to the stage of disease and the management options available to patients. Consideration will be given to the timing, delivery (by who), and format of the information. The quality checklist for qualitative data (NICE guidelines manual appendix I) will be used

Note any changes to the protocol or other considerations below

Review Protocol for section 2.4: What is the effect of smoking cessation on bladder cancer recurrence?

Clinical question section 2.4: Does smoking cessation affect outcomes for patients with bladder cancer?

Rationale:
Research shows that, compared to non-smokers, smokers have approximately three times the risk of developing bladder cancer. People who stop smoking reduce their risk of developing bladder cancer by 30-60% within four years.
Consultant urologists and nurses who work with patients with bladder cancer routinely ask patients about their smoking history when they first attend for assessment of their symptoms.
Patients who are current smokers, diagnosed with bladder cancer are given brief smoking cessation advice which includes an explanation about the increased risk of tumours recurring or becoming worse (progressing) in the future if they continue to smoke. If patients are likely to need cystectomy (removal of the bladder), they are advised to stop smoking to reduce the risk of complications of surgery (particularly chest infections) or, before radiotherapy to try to improve the effectiveness of radiotherapy. Patients are then signposted to smoking cessation services which provide behavioural and pharmacotherapy (medication) treatments.
Smoking cessation advice will usually be reinforced for patients who continue to smoke, typically during their annual health review by their General Practitioner and when they attend for their regular cystoscopies (bladder inspections).
Time of diagnosis would seem to be an ideal opportunity for motivating patients to stop smoking. However many health professionals are uncomfortable giving smoking cessation advice at this point, due to this time being one the key points in the patient pathway where increased psychological support is needed and patients often cite anxiety and stress as reasons for continued smoking or restarting smoking. As a result health professionals are uncertain when the best time is to give smoking cessation advice that will result in patients stopping smoking for the rest of their lives.
Although there is a large body of evidence which demonstrates the general health benefits on the heart and lungs of stopping smoking, some health professionals believe that smoking cessation advice given to patients diagnosed with bladder cancer would be more effective if specific reduction in risk of bladder cancer recurrence or progression rates could be demonstrated.
This review should demonstrate:
Does stopping smoking reduce the risk of tumour recurrence or tumour progression and if it does by how much?
How long does it take after stopping smoking for the risk of bladder tumours recurring or progressing to lower?
By how much does stopping smoking improve the effectiveness of radiotherapy to the bladder?
Does smoking cessation advice at time of diagnosis result in patients stopping smoking?
When is the most effective time to give smoking cessation advice that will result in patients stopping smoking permanently.

Please write a background in plain language explaining why we are asking the clinical question.
Include any relevant information that may help with reviewing the evidence such as:
Why is this topic contentious? Is there disagreement between healthcare professionals or variation in practice across the UK?
What are the benefits and harms of the alternative treatments or tests?
What kind of recommendations could you imagine yourself making following the evidence review?

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with diagnosed bladder cancer who have a smoking history	Smoking cessation	Smoking continued	Recurrence rate Overall survival Disease-specific survival Disease progression treatment-related morbidity Health-related quality of life (inc, patient reported outcomes)

Why are the outcomes listed in the above PICO important to patients?

Reduced risk of bladder cancer recurrence or progression if effective smoking cessation advice is given at the right time which results in permanent smoking cessation.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No date limit will be applied to the search
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No study design filters will be used as evidence is likely to come from case control and cohort studies.
List useful search terms.	Smoking cessation Reduction of risk of recurrence Reduction of risk of progression Timing of smoking cessation advice Smoking cessation and cancer diagnosis Tobacco exposure

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis	The evidence table for cohort studies will be used (NICE Guideline Manual Appendix K). The smoking status of participants will be important for this topic and data will be presented accordingly (i.e. ex-smoker, current smoker, time since smoking cessation, disease stage and grade). The timing of smoking cessation (e.g. before diagnosis, during treatment) will also be included if reported. Quality appraisal checklists for RCTs, case control studies and cohort studies will be used (NICE guideline manual Appendix D, E and F)

should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	

Note any changes to the protocol or other considerations below

Review Protocol section 3.1: What are the optimal endoscopic techniques for diagnosing new and recurrent bladder cancer (for example, the extent, depth and location of biopsies; white light, blue light, narrow band cystoscopy)?

Clinical question section 3.1: What are the most effective endoscopic techniques for diagnosing bladder cancer (for example white light, blue light, narrow band cystoscopy)?

Rationale:

The diagnosis of bladder cancer is usually made visually using a telescope inserted into the bladder (cystoscopy) with the patient awake as an outpatient. Until recently it was assumed that the standard procedure, white light cystoscopy (WLC) was accurate but it is now accepted that this will miss some bladder cancers. One particular type of bladder cancer called carcinoma in situ (CIS) although rare is easy to miss when using WLC.

There are two new techniques to aid the visual diagnosis of bladder cancer at cystoscopy – Photodynamic diagnosis (PDD) requires the instillation of a photosensitiser drug into the bladder by a nurse shortly before cystoscopy. This is preferentially taken up by bladder cancers that then fluoresce bright pink when a special blue light is used at cystoscopy. Narrow band imaging (NBI) uses a processor to filter out all but the blue and green light wavelengths. This has the effect of sharpening the contrast between normal tissue and bladder tumours. It does not require any prior preparation such as a photosensitiser.

The topic is contentious because both techniques are relatively new and only available in a small number of hospitals. There are no direct randomised trials to compare the two techniques against each other. Furthermore it is not known which groups of bladder cancer patients would benefit most from these techniques.

Such benefits include better visualisation of bladder cancers which are often multiple and may be hard to see under WLC. Theoretically better visualisation at the time of diagnosis would allow better surgical removal of all the bladder tumours and lead to a reduction in subsequent recurrences within the bladder as well as fewer cases of cancer progression. However both techniques also produce false positives. This means that patients can have a subsequent unnecessary surgical procedure. Both techniques are very safe for patients although PDD does require a nurse to instil the photosensitiser drug which has resource implications for staffing and theatres. The patients may also find the catheterisation uncomfortable. The benefits and the possibility of false positives should be discussed with patients in order for them to give informed consent.

This review should establish the overall effectiveness of PDD and NBI for diagnosing bladder cancer when compare with WLC and random bladder biopsies. The cost effectiveness of both techniques should be reviewed and guidance given as to which subgroups of bladder cancer patients would benefit most from these techniques.

Question in PICO format

Population	Index tests	Reference standard	Outcomes
Patients with suspected bladder cancer (new or recurrent)	White light cystoscopy Narrow band cystoscopy Blue light cystoscopy/ Photodynamic diagnosis (PDD) Alone or in combination	Histopathological examination of biopsied tissue	Diagnostic yield Sensitivity Specificity Process-related morbidity Health-related quality of life

Why are the outcomes listed in the above PICO important to patients?

The outcomes are important because better diagnosis may lead to fewer recurrences and hence fewer surgical treatments (Diagnostic yield and sensitivity). Patients should be aware of the false positive rate (specificity) whilst the morbidity of surgical intervention and its consequences are important to patients (morbidity and HR-QOL)

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	HTA (Mowatt, 2010) compared PDD with WLC for the detection of bladder cancer at the time of TURBT for newly diagnosed disease. We could update the HTA search which was conducted until March 2008 (would also need to search for narrow band imaging with no date limit).
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No study design filters will be used
List useful search terms.	Photodynamic diagnosis, PDD, narrow band imaging, NBI, bladder cancer diagnosis, blue light cystoscopy

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration	We will use the evidence table for diagnostic studies (NICE guidelines manual appendix K). The QUADAS quality checklist will be used (NICE guidelines manual appendix G), Where evidence allows the following subgroups will be analysed: diagnostic performance of the different PDD photosensitising agents type and grade of tumour patient/biopsy level analysis

handbook).	

Note any changes to the protocol or other considerations below
After discussion of the recommendations, the GDG suggested adding 'recurrence' as an additional outcome. A recent systematic review of raw data was suggested by the GDG (this was published after the search was completed by EH). This review was then included in the evidence review, to be discussed again at a later meeting.

Review Protocol for section 3.4: What is the most effective imaging for staging newly diagnosed and recurrent bladder cancer (e.g. ultrasound, CT, MRI)?

Clinical question section 3.4.1

In patients with new or recurrent bladder cancer is MRI more effective than CT for local staging and assessment of regional lymph nodes and can these tests be omitted in patients with NMIBC?

Question in PICO format

Populations	Test	Comparators	Outcomes
Low risk NMIBC High risk NMIBC MBIC	Pelvic CT PET-CT	Pelvic MRI (including multi-parametric MRI) No imaging (in NMIBC population only)	Sensitivity and specificity * for T3b or higher disease T2 or higher disease Local recurrence Regional lymph node metastasis Change in management Overall survival Progression free survival Morbidity associated with the test procedure

*Compared to reference standard of histopathology of surgical specimens or clinical/radiological follow up when there is no surgery.

Clincal question section 3.4.2

In patients with new or recurrent bladder cancer is CT more effective than IVU for the detection of upper tract involvement and can these tests be omitted in patients with NMIBC?

Question in PICO format

Populations	Test	Comparators	Outcomes
Low risk NMIBC High risk NMIBC MBIC	CT	IVU, No imaging (in NMIBC population only)	Sensitivity and specificity * for Presence of tumour in upper urinary tract Change in management Overall survival Progression free survival Morbidity associated with the test procedure

*Compared to reference standard of histopathology of surgical specimens or clinical/radiological follow up when there is no surgery.

Clincal question sect6ion 3.4.3
CT versus chest X-ray or PET-CT for thoracic malignancy
In patients with high risk NMIBC or MIBC is chest CT, chest PET-CT or chest X-ray the most effective method for the detection of thoracic malignancy and can these tests be omitted in patients with NMIBC?

Populations	Test	Comparators	Outcomes
High risk NMIBC MIBC	Chest CT	Chest X-Ray PET-CT NO imaging (in high risk NMIBC population only	Sensitivity and specificity * for thoracic malignancy Change in management Overall survival Progression free survival Morbidity associated with the test procedure

Clinical question section 3.4.4
CT versus MRI, PET-CT and bone scintagraphy for bone metastases
In patients with high risk NMIBC or MIBC is CT, MRI or bone scintagraphy the most effective method for the detection of bone metastses and can these tests be omitted in patients with NMIBC?

Populations	Test	Comparators	Outcomes
High risk NMIBC MIBC	CT	MRI bone scintagraphy No imaging (in high risk NMIBC population only	Sensitivity and specificity * for Bone metastases Change in management Overall survival Progression free survival Morbidity associated with the test procedure

Rationale:
Accurate staging of bladder cancer is important as tumour stage is key in determining the most appropriate treatment for an individual patient. Tumours are initially categorised as either muscle invasive or non muscle invasive, based upon histological analysis of specimens obtained at transurethral resection of the tumour. Non muscle invasive tumours are subcategorised as either high risk or low risk, dependent upon histological features. Low risk non muscle invasive disease makes up the largest group of patients with bladder cancer and these patients do not usually undergo any imaging staging (however, the evidence base for this requires review).
Patients with muscle invasive or high risk non muscle invasive tumours have a higher risk of tumour extension beyond the bladder wall, of spread to adjacent organs, of lymph node involvement and of distant metastases and these patients require imaging staging. At present in the UK, initial tumour staging is performed almost exclusively with either CT or MRI. There is generally considered to be little difference in the accuracy of these modalities in terms of staging of the primary tumour (T staging). MRI potentially gives a more detailed depiction of the layers of the bladder wall and of the pelvic organs but is more susceptible to artefact and patient intolerance and is more expensive. CT is quicker, cheaper and more available and allows the inclusion of staging of the chest and upper abdomen in the same examination, but uses ionising radiation. Newer MRI techniques such as tissue perfusion and diffusion-weighted imaging have the potential to increase the sensitivity and accuracy of the MRI examination. The modality used in each centre is dependent upon local availability, clinician and radiologist preference and possibly cost. CT and MRI have similar accuracies for detection of pelvic nodal metastases, however diagnosis is based predominantly

upon node size and this approach is well recognised as having limited accuracy. Nodal staging using MRI with superparamagnetic iron oxide as a contrast agent has shown increased accuracy over conventional MRI, but this agent is not currently available in the UK. Bone metastases generally occur in the context of more advanced disease and are often detected on CT or MRI, bone scan is potentially more sensitive but has limited specificity and is not used as part of routine staging in most centres.

Alternative imaging techniques for staging include PET/CT and ultrasound. The most commonly used PET tracer, 18F-FDG, is unsuitable for local staging of primary bladder tumours as the bladder wall is obscured by intense activity within the urine. However, 18F-FDG-PET/CT may be accurate in the diagnosis of nodal involvement or distant metastases. PET/CT using alternative tracers which are not excreted in the urine, such as 18F-choline, have been studied in the staging of bladder cancer, but these tracers are more expensive and not widely available. Ultrasound is cheap and widely available, but is generally considered to be inferior to CT and MRI in local bladder and pelvic nodal staging. However, ultrasound has the potential to detect small bladder tumours and is also useful in the evaluation of the upper urinary tracts for obstruction and may therefore have a role in certain subgroups. Ultrasound contrast agents may increase the accuracy of this technique. Intravenous urography has been replaced by CT in many areas of clinical practice, but is useful in the evaluation of the upper tracts, it may have a role to exclude ureteric obstruction and upper tract urothlial lesions, particularly in the low risk non muscle invasive group. Chest x-ray is also a cheap and universally available imaging technique, it is useful in the diagnosis of lung metastases and of primary lung cancer but is of lower sensitivity than chest CT, it may have a role in the work up of patients with newly diagnosed bladder cancer as these patients are often elderly and smokers and have an increased risk of lung cancer.

Diagnosis of recurrence of low risk non muscle invasive bladder cancer is almost exclusively made at cystoscopy. A non invasive imaging technique for diagnosis of recurrence is an attractive proposition, but would have to have a high sensitivity for detection of small tumours. Patients with recurrence of muscle invasive bladder cancer following radical radiotherapy or chemoradiotherapy will require imaging restaging to assess suitability for salvage cystectomy. Restaging is carried out with CT, MRI, PET-CT or a combination of these tests, with the extent of local invasion and the presence of pelvic nodal or distant metastases being important considerations. Early detection of local tumour recurrence following radiotherapy or chemoradiotherapy using a non-invasive imaging technique may also be advantageous and perfusion and diffusion weighted MRI and 18F-choline PET/CT have the greatest potential in this area.

This review should establish the relative accuracy of CT and MRI in the staging of muscle invasive bladder cancer, particularly with regard to recent development in MRI technique, such as perfusion and diffusion imaging. The role of these imaging techniques as well as PET/CT should also be established in the restaging of patients with bladder recurrence under consideration for salvage cystectomy. The role of imaging techniques for the early and accurate diagnosis of bladder recurrence following chemo/radiotherapy should be determined. Finally, evidence for the current practice of not performing imaging staging for low risk non muscle invasive bladder cancer patients should be reviewed.

Why are the outcomes listed in the above PICO important to patients?

The main consideration should be the diagnostic accuracy of the imaging investigations, followed by availability, cost, patient convenience and acceptability.

The morbidity of these imaging investigations is minimal. Radiation dose is a consideration, particularly in the low risk patients who have a good prognosis and may be subjected to repeated examinations, but the small risk of radiation dose is outweighed by the importance of accurate diagnosis in the other patient groups.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No, early CT and MRI studies from the 1980s onwards comparing with historic techniques may be relevant.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No study design filters will be used
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	We will use the evidence table for diagnostic studies (NICE guidelines manual appendix K). The QUADAS quality checklist will be used (NICE guidelines manual appendix G), Diagnostic accuracy will be defined by staging agreement or disagreement with the final TNM stage as identified by histopathology. Evidence will be stratified by the patient subgroups specified in the PICO.

Note any changes to the protocol or other considerations below

For Topic D1: a date limit of 1990 onwards was agreed with BT 31/10/2013. Also agreed to include PET/CT as an intervention and to exclude studies using 0.2 or 0.5-Tesla MRI scanners as these are not relevant to current practice

Review Protocol for section 3.2: What are the comparative patient outcomes for treating low-risk non-muscle invasive bladder cancer with:• Transurethral resection

Rationale:
Bladder cancer is a common disease comprised of at least two distinct types. These types reflect molecular pathways within the cancer and produce tumours with widely different outcomes. Low-grade bladder cancer is typically a non-invasive disease in which tumours recur frequently within the bladder following treatment, but rarely invade the wall or spread beyond the bladder to cause death. In contrast, high-grade bladder cancer is an aggressive disease. These tumours may be detected before or after the onset of muscle invasion, and before or after the tumour has spread beyond the bladder. The care of patients with non-muscle invasive high-grade bladder cancer is directed at preventing or detecting the onset of muscle invasion, before the cancer escapes from the bladder. Invasive cancers typically require radical treatment if cure is to be obtained.

The accessibility of the bladder through the urethra, means that bladder cancers may be treated by endoscopic excision. This transurethral resection may remove the cancer in its entirety or just confirm the nature of a cancer before further treatment. This Topic will focus upon the practice of transurethral surgery for non-muscle invasive bladder cancers. Patients with these cancers often develop further bladder tumours following removal of their first lesion. These further tumours represent either residual disease (part of the previous cancer at the same location), recurrences related to the previous bladder cancer but spread to a different part of the bladder or new primary bladder cancers unrelated to the previous tumours.

The risk of further cancers within the bladder or of progression to invasive cancers reflects many factors. These may be related to the type of disease (e.g. low or high grade disease, tumours affecting single or multiple parts of the bladder), the patient (e.g. inherited genetic profile, continued or stopped carcinogen exposure) or the practice of transurethral surgery. Some surgeons feel that the practice of transurethral surgery needs to be standardised to all cancers, and include steps such as biopsying normal looking bladder wall to look for occult abnormal tissue. Others suggest that surgeons should be able to react to each tumour individually and tailor the practice of transurethral surgery accordingly. Case series and randomised trials have identified features related to the tumour and the surgeon that predict future outcomes.

This review will look at the aspects of surgical practice that may affect the subsequent behaviour of new or recurrent non-muscle invasive bladder cancers. This review should establish in which types of tumours the different techniques of transurethral surgery are recommended and identify standards defining good quality transurethral surgery.

Question in PICO format

Clinical question section 3.2.1. Does the technique of transurethral surgery in new or recurrent bladder cancer influence outcomes?

Population	Intervention	Comparison	Outcomes
Patients with bladder cancer (new or recurrent)	Transurethral resection with muscle	Transurethral resection without muscle	Recurrence Progression Residual tumour rate Treatment-related

			morbidity Health-related quality of life, inc patient reported outcomes

Clinical question section 3.2.2. Does random biopsy affect outcomes in people with non-muscle invasive bladder cancer?

Population	Intervention	Comparison	Outcomes
Patients with NMIBC (new or recurrent)	Transurethral resection with random biopsies	Transurethral resection without random biopsies	Recurrence Progression Residual tumour rate Treatment-related morbidity Health-related quality of life, inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?
Recurrence and progression reflect different measures of the behaviour of non-muscle invasive bladder cancer. For the patient, events in each represent the need for further treatment and a worsening in the prognosis of the cancers. Residual tumour rate and the presence of detrusor muscle (or other pathological factors) may reflect the quality or completeness of transurethral surgery. Treatment related morbidity and quality of life outcomes are important to patients as they affect and measure their quality of life.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No date limits will be applied to the search
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No study design filters will be used as evidence will come from case control or cohort studies
List useful search terms.	Mostly the words mentioned in the PICO

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Data will be extracted regarding the patient population, stage/grade of cancer, and whether it is recurrent or newly diagnosed. Non-comparative data will be considered if insufficient comparative data. Quality checklists from the NICE guidelines manual will be used as appropriate e.g. cohort study checklist. Data will be pooled where appropriate. Surgical experience of the surgeon may be an important consideration if reported.

Note any changes to the protocol or other considerations below

Review Protocol for section 3.3: What is the most effective technology involving a urine test for identifying new and recurrent bladder cancer?

Clinical question section 3.3: What are the diagnostic accuracies of urine testing technologies for new and recurrent bladder cancer?

Rationale:

Urine examination for bladder tumours includes conventional cytological examination and the relatively limited use of adjunctive tools (no longer new, they have been around for at least 5-10 years!) such as NMP22, FISH (UroVysion) and ImmunoCyt (in USA, not in the UK). Although other urine tests are in development, none are yet routinely available and there is insufficient evidence to consider them at this time.

Cytology has stood the test of time in spite of only a moderately high sensitivity for high grade tumours (70-75%) and low sensitivity (20-50%) for low grade tumours. The strength of urine cytology lies in its high specificity (>95%) for the clinically more important high grade tumours. This is achieved in experienced hands, however, the quality of cytology services in general, is perceived to be variable.

The need for higher sensitivity in detection of tumours (new and recurrent) has driven the search for a test that would either supplement or replace urine cytology. The topic is contentious because urine cytology despite the above limitations is relatively cheap and easily accessible while the use of markers is associated with additional cost and expertise in interpretation and of uncertain benefit, particularly if used without cytology.

Ultimately, a highly reliable urine test might reduce the need for cystoscopy in follow up of bladder tumours. This would present considerable benefit to patients and may result in cost savings.

NMP22 (available as near-patient test kits (positive or negative result) as well quantitative assays (with variable ranges) performed in the chemical pathology lab) shares many of the limitations of urine cytology (false positives with infection, stone disease, post-treatment and instrumentation of the urinary tract) but reported to have a higher sensitivity than that of urine cytology. The specificity of urine cytology, particularly for high grade tumours remains vastly superior to NMP22. Replacing urine cytology with a marker like NMP22 would pose a serious disadvantage due to the loss of specificity. NMP22 may be used to triage cases for cytology which would improve the sensitivity of detection of tumours without loss of specificity.

Reflex testing of atypical (not diagnostic of malignancy) cytology with UroVysion has recently been shown to be of great advantage. As this is a genetic test, it does not suffer from the limitations of cytology and NMP22 (infection, stones, post-treatment and instrumentation). UroVysion test is shown to have a high negative predictive value (hence, potential use as a 'test of cure'). Recurrence of a positive UroVysion test following intravesical BCG treatment has recently been shown to be associated with disease progression. This marker holds the best prospect in diagnosis as well as follow up of bladder tumours in conjunction with a high quality urine cytology service.

The cost of urine cytology is approx. £100 while that of UroVysion is approx. £150 and requires the use of Liquid based cytology (LBC eg. ThinPrep) and fluorescence microscopy which would require referral of the test to a specialist cytology/cytogenetics lab. However, this test is available/accessible to most cancer centres which manage patients with bladder tumours.

ImmunoCyt requires immunostaining (with all its limitations relating to expense and

expertise) in addition to fluorescence microscopy and is reported to be less sensitive and specific than UroVysion while being much more labour intensive.
It would be useful to recommend a high quality of urine cytology services that practises clinical audit and a quality improvement programme. Comparison between the sensitivity of markers in the setting of a good cytology service (sensitivity and specificity at the higher end of reported figures) would demonstrate that markers such as NMP22 offer little overall advantage over cytology.
The value of using markers in defined clinical settings eg investigation of haematuria (new cases) and follow up of patients under surveillance for bladder tumours (recurrent cases) would be a valuable recommendation if supported by available evidence.
It would be useful to examine the evidence in order to make recommendations under the following clinical scenarios-
Role of markers (NMP22) in replacing or triaging cases for cytology
Role of markers (UroVysion, ImmunoCyt) in assisting cytology in clarification of atypical (not diagnostic of malignancy) cases
Role of markers (UroVysion) in predicting recurrence and progression of bladder tumours following treatment where cystoscopic / cytological follow up is currently the standard of care.

Question in PICO format

Population	Index tests	Reference standard tests	Outcomes
Patients with suspected bladder cancer (new or recurrent)	Urinary cytology Nuclear matrix protein (NMP22) FISH (UroVysion) ImmunoCyt	Cystoscopy & biopsy	Diagnostic yield Sensitivity Specificity

Why are the outcomes listed in the above PICO important to patients?
The reliable detection of a new or recurrent bladder tumour by a non-invasive test such as urine examination (cytology alone or with a marker) would reduce the need for invasive investigations and also minimise the delay in patients receiving treatment

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Sources searched in the HTA will be identified.
Can we apply date limits to the search	A Health Technology Assessment (Mowatt, 2010) relevant to this topic was published in 2010. We will update the HTA search which was conducted up until March 2008.
Are there any study design filters to be	No study design filters will be used

used (RCT, systematic review, diagnostic test).	
List useful search terms.	Search terms will be identified from the published HTA. Urine cytology, urinary biomarkers, NMP22, UroVysion, ImmunoCyt

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	We will use the evidence table for diagnostic studies (NICE guidelines manual appendix K). The QUADAS quality checklist will be used (NICE guidelines manual appendix G), which was also used in the HTA. The following levels of analysis were reported in the HTA and will be considered in the evidence review: Patient level, specimen level, and stage/grade. Also if urine sample was voided or obtained by bladder wash. Meta-analysis of diagnostic studies will be performed if appropriate

Note any changes to the protocol or other considerations below

Review Protocol for section 4.1: Which factors determine risk of relapse and progression in newly diagnosed non-muscle invasive bladder cancer (e.g. histological grading of bladder cancer)?
Clincal question section 4.1.1: ***In addition to the factors specified in the EORTC risk tables, do TCC variants, differentiation of TCC and lymphovascular invasion predict recurrence and progression after treatment?***

Rationale:
Most patients with bladder cancer have a tumour that involves the surface lining of the bladder (urothelium), or the connective tissue layer (lamina propria) that connects the surface lining to the main muscle coat. These tumours are designated stages pTa and pT1 respectively, and they are also classified according to whether they are regarded as aggressive, moderately aggressive, or not aggressive, grades 3, 2 and 1 respectively.
These tumours may return on the urothelium (recurrence), or worsen, meaning return and extend to involve the main muscle coat of the bladder (progression).
In general, recurrence is a problem for patients (because any tumour recurrence raises the concern that the cancer will progress and/or spread) and for the NHS (because of the need to provide capacity for treatment of recurrence), but it does not threaten patients' lives. In contrast, progression does threaten patients' lives, because if the muscle coat of the bladder becomes involved with cancer, between 20 and 25 out of 100 such patients will have spread into their lymph glands, and their chance of cure falls sharply.
We have some pathological markers of the risks of recurrence and progression, such as stage, grade, and the presence of carcinoma *in situ*, and other clinical markers, such as tumour size, number and the presence of recurrence at three months from the initial resection. On the basis of EORTC chemotherapy study data, it was suggested many years ago that the management of LRNMIBC could be streamlined significantly by the use of two easily established clinical variables alone, namely whether the initial tumour is solitary or multifocal, and whether there was recurrence or not at three months. Despite the evidence base for this, and its ease of assessment, it has not become widely used in the NHS.
So the use of these factors remains unsatisfactory for an individual patient, and does not predict the individual risks of recurrence and progression. Molecular markers (such as EGFR) have been studied for over 20 years, to see if some laboratory studies are able to be useful in clinical practice, but none has emerged as useful to the NHS.
If we knew better for individual patients about their risk of recurrence and particularly progression, it would be possible to inform the discussion of the cancer risk, which is one of the pillars of the discussion about which treatment option is best for a given patient. Many patients would consider better forecasting of their own personal cancer risk to be a very useful step forward.

Pathological findings play a central role in the clinical management of bladder tumours with the listed prognostic factors (under PICO) playing an important part in indicating poor prognosis (lymphovascular invasion) and likelihood of poor response to chemo/radiotherapy (squamous and glandular differentiation). There is, however, insufficient information on the value of individual factors eg. histological subtypes: does squamous cell carcinoma of the bladder carry a worse prognosis than urothelial (transitional cell) carcinoma all other factors being the same?
Why is this topic contentious? Is there disagreement between healthcare professionals or variation in practice across the UK?
The topic is contentious for the reasons given above. There is variation in practice in

applying these criteria when determining clinical management and is based on experience of groups of clinicians rather than on a validated scoring system such as those available for cancers at other sites (eg. Leibovich score in prostate cancer). We know that recurrence and progression are major problems for patients and for the NHS, but we struggle with individual patients to predict them.

What are the benefits and harms of the alternative treatments or tests?
In the absence of reliable molecular signatures, there are currently no good alternatives to the listed clinical and pathological data in predicting recurrence or progression of bladder tumours.
Do any of the listed prognostic factors (under PICO) in univariate or multivariate analysis indicate a worse prognosis that calls for a more aggressive approach in the management of NMIBC eg. early cystectomy for multifocal CIS or for aggressive variants of urothelial carcinoma such as micropapillary and nested variants. Does histological grading WHO2004 offer better information in clinical management than WHO1973? Does persistent positive urine cytology following treatment confer a worse prognosis? Can the progression of cancer stage T1 to T2 be reliably predicted by subdivision of T1 into a, b ,c or into microscopic and extensive (van Rhijn, 2012)?

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with newly diagnosed NMIBC	Prognostic factors: EORTC risk factors TCC variants (micropapillary and nested patterns) TCC differentiation (squamous, glandular and sarcomatoid) Lymphovascular invasion	N/A	Disease specific survival Recurrence Overall survival Disease progression

Why are the outcomes listed in the above PICO important to patients?
It is important to identify patients who are at risk of progressing from NMIBC to MIBC as the latter requires radical treatment and is associated with a reduced lifespan and poor QALY.
Recurrence matters to patients because not only does it always raise concern that this might be the first sign of the disease becoming harder (or impossible) to cure, but it also means that further time and discomfort are needed as part of the process of getting rid of the recurrence
Progression matters to patients because it indicates disease that significantly threatens their life, and it will mean that much more intensive and usually invasive treatment is needed, with the associated time out of daily life, discomfort or pain, anxiety about success and treatment-related adverse effects and the impact of treatment on daily life.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.

Can we apply date limits to the search	No date limit will be applied to the search
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No study design filters will be used
List useful search terms.	Subdivision of stage T1 bladder cancer, histological grading of bladder cancer, micropapillary variant, nested variant of urothelial carcinoma, multifocal CIS bladder

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	We will use the evidence table for prognostic studies (NICE guidelines manual appendix K). The prognostic study checklist will be used (NICE guidelines manual appendix J).

Note any changes to the protocol or other considerations below

Review Protocol for section 4.2: What are the comparative patient outcomes for treating low-risk non-muscle invasive bladder cancer with: Intravesical chemotherapy

Clinical question section 4.2.1: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle invasive bladder cancer?

Rationale:
Most patients with bladder cancer have a tumour that involves the surface lining of the bladder (urothelium), or the connective tissue layer (lamina propria) that connects the surface lining to the main muscle coat. These tumours are designated stages pTa and pT1 respectively, and they are also classified according to whether they are regarded as aggressive, moderately aggressive, or not aggressive, grades 3, 2 and 1 respectively.

Stage pTa tumours that are G1 and G2 are likely to return on the urothelium (recurrence), but are very unlikely to worsen (progression), meaning either becoming G3, or pT1 (or higher stage). These tumours are therefore regarded as low-risk non-muscle invasive bladder cancer (LRNMIBC), because of the low risk of progression. The risk of recurrence in LRNMIBC, however, is a problem for patients (because any tumour recurrence raises the concern that the cancer will progress and/or spread) and for the NHS (because of the need to provide capacity for treatment of recurrence).

The risk of recurrence can be reduced by the administration of chemotherapy medication, in liquid form, into the bladder (intravesical chemotherapy). This can be done immediately, or shortly after telescopic removal of the tumour (transurethral resection), and subsequently, as a planned outpatient procedure. Several different chemotherapy drugs have been used, and studied.

There is debate (and variation) about which patients with which sort of LRNMIBC should be treated with intravesical chemotherapy, including whether patients with small or very small tumours should be treated, and what sort of recurrent tumours should be treated.

The advantage of not being treated is that no side effects of treatment are suffered, whereas the benefit of being treated may be that recurrence becomes less likely. The disadvantage of not being treated is that there is no reduction in the risk of recurrence, and the disadvantage of being treated is that side effects (such as urine infection, bladder pain, and genital rashes) are suffered.

Instillation of BCG vaccine is also offered to some patients who have recurrence of LRNMIBC following previous intravesical chemotherapy. The side effects of BCG include irritation of the bladder, urine infection, occasional rare consequences probably related to the effects of BCG on the body's immune system, and very rare infections with the BCG bacteria. These side effects need to be considered in a consideration of the advantages and disadvantages of BCG equivalent to the consideration of the advantages and disadvantages of intravesical chemotherapy.

The topic is being considered because LRNMIBC is common, recurrence is common, and because intravesical chemotherapy has significant efficacy, but the pattern of disease is not homogeneous, meaning the grade, size, number and recurrence history of tumours can combine to present a significantly mixed group of patients and tumours, so that determining which patients with which tumours should be treated is an important area for guidance.

Recommendations for patients with LRNMIBC are likely to address:

which patients with new tumours should be offered treatment (and which should not)
which patients with recurrent tumours should be offered treatment (and which should not)
which drugs should be recommended (and which should not)
which regimens should be recommended (and which should not)
which patients with recurrent tumours should be offered BCG (and which should not)

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with newly diagnosed NMIBC following first TUR Subgroups male/female: Low/intermediate-risk NMIBC High-risk NMIBC	Intravesical chemotherapy/BCG Single installation Induction course Maintenance BCG Mitomycin C Epirubicin Doxorubicin (adriamycin) Gemcitabine Eoquin	Each other None	Overall survival Disease-specific survival Disease progression recurrence Treatment-related morbidity Treatment-related mortality Health-related quality of life inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?

Cancer outcomes are the most obvious outcome of relevance because successful treatment of the cancer is what the treatment is being given for.

HRQoL is a crucial outcome, because "the price" of successful cancer treatment is a fundamental part of the weighing up of treatment options that patients do

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	Is there a date when intravesical therapy became common practice? Common clinical practice from around the mid 1990s, but studied for the mid 1980s
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	A RCT/systematic review filter will be used There is sufficient RCT data to make this reasonable
List useful search terms.	Intravesical Chemotherapy Immunotherapy Mitomycin C Epirubicin

	Doxorubicin Gemcitabine BCG

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	The evidence table for intervention studies will be used (NICE Guideline Manual Appendix K) Quality checklists for RCTs (NICE manual Appendix D) and meta-analysis and systematic reviews (NICE manual Appendix C) will be used Evidence will be analysed by gender and risk subgroups where appropriate. Consideration will be given to immediate single installation therapy, induction therapy and maintenance therapy. Intravesical chemotherapy agents will be analysed together with specific agents included as subgroups.

Note any changes to the protocol or other considerations below

Review Protocol for section 4.2.2: What are the comparative patient outcomes for treating low-risk non-muscle invasive bladder cancer with: Transurethral resection

Clinical question section 4.2.2: In patients with recurrent bladder cancer and previous low risk bladder cancer does treatment without histological sampling affect outcome?

Rationale:
Bladder cancer is a common disease comprised of at least two distinct types. These types reflect molecular pathways within the cancer and produce tumours with widely different outcomes. Low risk bladder cancer is a low grade (well differentiated), non-invasive disease in which tumours recur frequently within the bladder following treatment, but rarely invade the wall or spread beyond the bladder to cause death. As such, patients with low risk bladder cancer often develop recurrences within the bladder and for most these are identical to the previous low risk cancer. When analysed, around 80% of tumors remain similar in type to the previous bladder cancer. Furthermore, the use of regular cystoscopy to survey the bladder means that many recurrences may be detected whilst small.

Treatment of low risk bladder cancer recurrences may be with endoscopic resection to remove the cancer, fulguration by electrocautery or laser energy to destroy the cancer in situ (with or without biopsy), intravescial chemotherapy (also known as chemoresection) or merely observation (so called active surveillance). The former allows pathological evaluation of the cancer and may be necessary to remove tissue from large tumors, but requires regional or general anaesthesia and a rigid cystoscopy and bladder resection. Consequently, the risks of intervention are higher than for fulguration (which may performed under local anaesthesia), chemotherapy or active surveillance. However, these other approaches do not sample the tissue of the cancer recurrence and could miss the minority of cases in which the cancer is becoming more aggressive. Also these approaches are less effective at removing the cancer and so could lead to higher recurrence (or residual cancers) rates and more post-treatment symptoms.

In this review we will evaluate each approach to treating recurrence within the bladder following a previous low risk bladder cancer. We will attempt to determine in which patients the benefits of transurethral resection outweigh the risks from the treatment and from the cancer. We will attempt to identify low risk cancers in which the rate of disease progression is higher and so the evaluation of tissue is necessary for patient safety. We will look to identify tumors in which less intensive intervention is sufficient and to compare the outcomes of the different approaches.

Population	Intervention	Comparison	Outcomes
Patients with recurrent bladder cancer and previous low risk NMIBC	Treatment with histological sampling e,g, cystocopy & biopsy or TUR	Treatment without histological sampling e.g cystodiathermy	Recurrence Progression Residual tumour rate Treatment-related morbidity Health-related quality of life, inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?
Recurrence, residual tumour rate, progression reflect different measures of the behaviour of low risk non-muscle invasive bladder cancer. For the patient, events in each represent the need for further treatment or a worsening in the prognosis of the cancers. Treatment related morbidity and quality

of life outcomes are important to patients as they affect and measure their quality of life.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science and Biomed Central. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No date limits will be applied to the search
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No filter
List useful search terms.	The PICO words

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Data will be extracted regarding the patient population, stage/grade of recurrent cancer and previous treatment received. Non-comparative data will be considered. Quality checklists from the NICE guidelines manual will be used as appropriate e.g. cohort study checklist. Data will be pooled where appropriate. The quality of the TUR/biopsy is likely to be an important consideration inc presence of muscle in the sample.

Note any changes to the protocol or other considerations below
A date limit was applied to the search (from year 2000 onwards) due to the large number of papers that were picked up by the search with no date limit.

Review Protocol for section 4.2.3: What are the comparative patient outcomes for treating high-risk non-muscle invasive bladder cancer with:

- ***Transurethral resection***

Clinical question section 4.2.3: Does re-resection in high risk NMIBC influence outcomes?

Rationale:

High-grade non-muscle invasive (HGNMI) bladder cancer is an aggressive disease. The natural history of these cancers can be difficult to predict. Around 1 in 4 will progress to invade the bladder wall and may eventually spread beyond the bladder. Radical treatment, by either bladder removal (cystectomy) or radiotherapy, is necessary for tumours invading the bladder wall if cure is to be obtained. Whilst all patients with HGNMI bladder cancer are followed closely after initial treatment, a proportion of tumours progress to invasion and spread without detection. The risk of progression to invasion, or recurrence of another HGNMI cancer within the bladder, is related to several factors. These include pathological features of the tumour, patient factors and the practice of endoscopic transurethral resection. Whilst most surgeons agree on the need for an initial tumour resection, there is controversy regarding the role of an early, planned re-resection. This normally occurs within 6 weeks of the initial transurethral resection. It should reassess the site of the initial cancer and sample the urothelium within the bladder/prostatic fossa.

Advocates of re-resection report that a proportion of HGNMI tumours are found to actually be invasive upon re-assessment, and that pathological features missed in the initial resection may be detected. Furthermore, residual disease at re-resection is known to be a is a poor prognostic feature for the patient and may alter treatment plans. However, in many patients re-resection does not influence their treatment and adds cost to the healthcare provider and the risks of further surgery to the patient. Furthermore, some surgeons feel that the emphasis should be on an initial high-quality resection, so that all pathological factors and all invasive tumours are identified at this time. They argue that the re-resection delays the time to reaching a final pathological diagnosis.

This review will assess the evidence for re-resection in HGNMI bladder cancer and identify in which patients and tumours it is beneficial. It will identify measures of high quality re-resection that should be achieved by this procedure.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with newly confirmed high risk NMIBC following first TUR	Re -resection	No –re-resection	Recurrence Progression Disease-specific survival Radical treatment Change/accuracy of staging Residual tumour rate Process-related morbidity Health-related quality of life inc. Patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?

Recurrence and progression reflect different measures of the behaviour of non-muscle invasive bladder cancer. For the patient, events in each represent the need for further treatment and a worsening in the prognosis of the cancers. Radical treatment rates reflect the need to treat the cancer more aggressively and carry a high risk of complications and side effects for the patient. Residual tumour rate and

upstaging may reflect the quality or completeness of transurethral surgery. Process related morbidity and quality of life outcomes are important to patients as they affect and measure their quality of life.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No date limits will be applied to the search
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No study design filters will be used
List useful search terms.	BCG, Re-resection, High grade bladder cancer, NMI bladder cancer

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Evidence tables for intervention studies will be modified according to this PICO. We will include comparative studies of patients undergoing re-resection or no re-resection. Quality checklists for cohort studies and case-control series will be used where appropriate (NICE Guidelines manual Appendix E and F. The quality of the first TUR is likely to be important.

Note any changes to the protocol or other considerations below

Review Protocol for section 4.2.4: What are the comparative patient outcomes for treating high-risk non-muscle invasive bladder cancer with:

radiotherapy
intravesical BCG
radical cystectomy with urinary stoma or bladder reconstruction?
Clinical question 4.2.4: For which patients with non-muscle invasive bladder cancer would primary cystectomy produce better outcomes than BCG?

Rationale:
High-grade non-muscle invasive (HGNMI) bladder cancer is an aggressive disease. The natural history of these cancers is difficult to predict. Around 1 in 4 will eventually progress to invade the bladder wall and may spread beyond the bladder to cause death. Invasion marks a dramatic worsening in prognosis for the patient and needs aggressive treatment if cure is to be obtained. Whilst various pathological factors can be used to guide the risk of developing invasion from a HGNMI tumour, none offer absolute certainty to the patient.

Currently, many urologists offer an initial treatment of BCG immunotherapy for HGNMI bladder cancer. BCG may reduce the chance of a tumour progressing to invasion but has side effects and can delay the identification of worsening cancers. This delay may affect the cure rate for aggressive cancers. Advocates of BCG suggest this treatment may reduce progression rates for individual tumours, allows the identification of patients with non-progressing cancers (and so these patients do not receive radical treatment) and is safe if the bladder is monitored closely. In contrast, other physicians claim that BCG is not effective at reducing progressing and delays the identification of worsening disease such that it reduces the chances of cure in the patients. An alternate approach to BCG is primary radical treatment (usually cystectomy) for HGNMI cancers. This may be the safest option for patients, but will lead to over treatment for those whose cancers would not progress to invasion and carries the risks of major surgery or radiotherapy. Although radical radiotherapy / chemo-radiotherapy is used to treat muscle invasive bladder cancer, evidence to support its use in the HGNMI disease is less compelling. Various pathological and clinical factors may be used to guide the risk of progression and the treatment options.

This review will look at the evidence of BCG and primary radical treatment (cystectomy) for HGNMI bladder cancer. It will estimate the risks and benefits of each approach and try to identify factors that would be useful in aiding patient choice.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients diagnosed with high risk NMIBC with no prior BCG therapy Subgroups: male/female Pathology features Solitary tumour Multifocal tumour Extent of Lamina propria involvement Presence of CIS	Primary Cystectomy Primary Radiotherapy/chemoradiotherapy	BCG therapy	Overall survival Disease-specific survival Metastasis free survival Bladder preservation rates treatment related mortality treatment related morbidity Health-related quality of life, inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?
Overall, disease-specific and metastases-free survival are important outcomes for patients. Each represents an adverse outcome and perhaps treatment failure. Treatment related morbidity, mortality and quality of life outcomes are important to patients as they affect and measure their quality of life. Bladder preservation rates are a measure of the success of a bladder sparing approach, generally representing optimised patient quality of life.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	Is there a date when BCG became common clinical practice? Answer: 1990s
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No filter
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	The evidence table for intervention studies will be used (NICE Guideline Manual Appendix K) Quality checklists for RCTs (NICE manual Appendix D) and meta-analysis and systematic reviews (NICE manual Appendix C) will be used Evidence will be analysed by gender and the subgroups specified in the PICO where possible. RCT data will be pooled when appropriate and risk ratios presented for the identified outcomes.

Note any changes to the protocol or other considerations below

Randomised trials and comparative studies were initially included in the evidence review. After discussion with the subgroup it was decided to also include the two largest series or patients (one cohort of patients treated with BCG and one treated with cystectomy) in order to benchmark the comparative studies.

Review Protocol for section 4.2.5: What are the comparative patient outcomes for treating high-risk non-muscle invasive bladder cancer with: Intravesical chemotherapy, Intravesical Bacille Calmette-Guerin (BCG), Radiotherapy, Radical cystectomy with urinary stoma or bladder reconstruction

Clinical question 4.2.5: What is the optimum treatment for patients with non-muscle invasive bladder cancer who have failed BCG?

Rationale:
Intravesical BCG is an immunotherapy used to treat intermediate and high-risk non-muscle invasive bladder cancer. This therapy may be administered as either a single 6 week course (known as "induction BCG") or as repeated instillations episodically for several years (known as "maintenance BCG"). Each treatment includes the instillation of live BCG bacteria, of which various strains are known to exist, into the bladder. Failure to respond to BCG occurs when a further bladder cancer arises following or during BCG treatment. These cancers may be better, similar or worse to the original tumour, and may be detected during, shortly after, or many years following BCG treatment. Therefore the term BCG failure includes a wide spectrum of events. It can also include patients who did not complete their treatment due to BCG related side effects (called BCG intolerant). In general most physicians agree that the development of tumour with muscle invasion following or during BCG treatment requires radical treatment (ether bladder removal; (cystectomy) or radiotherapy) if cure if to be obtained. In contrast, there is less consensus regarding the treatment of BCG failure when the disease is not muscle invasive. Some physicians feel that the timing of failure (early versus late) is important, whilst other feel that failure at any time requires more aggressive treatment.

Whilst radical cystectomy is perceived as the gold standard treatment for BCG failure, it may be over treatment in some patients and other patients are keen to avoid bladder removal regardless of risks. Therefore "bladder-sparing" treatments are reported for use in this context. These include immunotherapies (e.g. repeated BCG instillations with or without additional immune modulator), intravesical chemotherapy (such as gemcitabine), device assisted intravesical chemotherapy (e.g. mitomycin-c administration using EDMA or hyperthermia) and radiotherapy. These approaches avoid removal of the bladder, but carry the risk that the tumour may not respond and will progress to invasion or spread beyond the bladder. They also have side effects and toxicity. Given the spectrum of events encompassed by the term BCG-failure, it is possible that different treatments will be better for different types of failure.

This review will compare different treatments for patients who fail BCG. It will identity the risks and benefits of each treatment and try to identify if some are more suited to certain types of BCG failure.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients diagnosed with NMIBC who have failed BCG Subgroups: Male/female Pathology features Solitary tumour Multifocal tumour	Intravesical chemotherapy Radiotherapy/chemoradiotherapy Cystectomy BCG therapy Interferon Cystoscopy	Each other	Overall survival Disease-specific survival Metastasis free survival Bladder preservation rates treatment related mortality treatment related

Extent of Lamina propria involvement Presence of CIS			morbidity Health-related quality of life, inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?
Overall, disease-specific and metastases-free survival are important outcomes for patients. Each represents an adverse outcome and perhaps treatment failure. Treatment related morbidity, mortality and quality of life outcomes are important to patients as they affect and measure their quality of life.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	Is there a date when BCG became common clinical practice? (lot of studies 90's)
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No RCT filter
List useful search terms.	BCG failure, BCG refractory, BCG resistance, BCG intolerant, Gemcitabine, BCG and Interferon, Low dose BCG, Hyperthermia, EDMA? radiotherapy

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	The evidence table for intervention studies will be used (NICE Guideline Manual Appendix K) The nature of initial BCG failure will be of relevance to this topic Quality checklists for RCTs (NICE manual Appendix D) and meta-analysis and systematic reviews (NICE manual Appendix C) will be used Evidence will be analysed by gender and the subgroups specified in the PICO where possible. RCT data will be pooled when appropriate and risk ratios presented for the identified outcomes.

Note any changes to the protocol or other considerations below

Review Protocol for section 4.3: What specific interventions are most effective for patients with bladder toxicity following radiation or BCG therapy?

Clinical question section 4.3: ***What is the most effective intervention for bladder toxicity following radiotherapy or BCG therapy for bladder cancer?***

Rationale:

Radiotherapy and intravesical BCG (BCG vaccine inserted into the bladder), treatments used for high risk bladder cancer that is confined to the bladder can result in patients being cured of their cancer and with their bladder preserved but with significant side effects which can result in patients having a poor quality of life.

Irritative urinary symptoms (urinary frequency, urgency and pain when passing urine) are usually experienced by most patients for approximately 48 hours following intravesical BCG and for some weeks after radiotherapy. However for some patients these side effect s continue long term.

The cause of long term side effects of radiotherapy to the bladder or intravesical BCG may include bladder inflammation, abnormal blood vessel development within the bladder or scarring in the bladder. Consequently the bladder may be unable to store significant quantities of urine resulting in patients passing small volumes of urine frequently and urgently during the day and night, pain passing urine and blood in urine. These symptoms can develop up to 20 years after completion of radiotherapy to the bladder.

These side effects can be so bad that patients as a last resort have their bladder removed or have a urinary catheter (rubber tube with is inserted into the bladder to drain urine) fitted permanently.

Standard medications which aim to reduce symptoms of urinary frequency and urgency have varying effect and also have significant side effects, such as blurred vision, dry mouth etc. which some patients are unable to tolerate.

Most bleeding which occurs as a side effect of radiotherapy will stop without any need for treatment. Standard treatment for bleeding that does not settle of it's own accord would be electrodiathermy (cauterisation using an electric current that creates heat to destroy the bleeding area in the bladder). Treatments for severe bleeding include application of formalin orsilver nitrate to the bleeding area within the bladder, or bladder irrigation with alum. This is effective in stopping the bleeding but has a small risk of aluminium toxicity which may result in patients needing kidney dialysis.

Severe bleeding can also be treated by embolising arteries that supply the bleeding area in the bladder. This is a procedure that can be time consuming and technically difficult as it is done by a specially trained Radiologist who uses xrays to identify the correct arteries before injecting them with an agent which will block the arteries to remove the blood supply from the area that is bleeding.

It is recommended that during treatment with intravesical BCG, Irritative urinary symptoms that last longer than 48 hours should be treated with oral Isoniazid (antibiotics to treat tuberculosis) until symptoms have resolved. There is however, some evidence that suggests prophylactic Isoniazid or Ofloxacin (antibiotics to treat tuberculosis) may reduce the number of patients having significant long term side effects of intravesical BCG treatment, but this is not currently standard treatment.

There is early research which shows that Botox injections under the lining of the bladder are effective at improving the Irritative urinary symptoms as a side effect of radiotherapy.

Approximately two thirds of patients do not manage to complete the full course of BCG due being unable to tolerate the Irritative urinary symptoms. Rather than stopping treatment, some urologists recommend giving patients a reduced dose of BCG or giving it less frequently. Giving a reduced dose is controversial as it is not possible to accurately measure a reduced dose e.g. half or a third due the mixing and administration equipment used. E.g. Immucyst is mixed in a prefilled 50ml bag of sodium chloride 0.9%, it would only be possible to estimate half.

New treatments such as intravesical sodium hyaluronate (Cystistat®) and Elmiron are emerging which claim to alleviate Irritative urinary symptoms and improve bladder capacity. The manufacturers suggest either instilling cystistat into the bladder following each BCG treatment to

prevent long term side effects of BCG, as treatment of irritative urinary symptoms following BCG or radiotherapy . Although having been used effectively for some time for the treatment of recurrent bacterial cystitis and interstitial cystitis, as yet there is a lack of research to demonstrate their effectiveness for side effects of radiotherapy or intravesical BCG therapies.
It is expected that this review will identify effective methods to reduce the risk of long term side effects of radiotherapy to the bladder and make recommendations for the standardisation of treatment for significant long term side effects which occur as a result of radiotherapy to the bladder or intravesical BCG.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients who develop bladder toxicity following radiotherapy or BCG therapy for bladder cancer	Interventions for bladder toxicity: Cystectomy Isoniazid Ofloxacin Cystistat Elmiron Anticholinergics Botox Alum Formalin Embolisation Catherisation Hyperbaric oxygen Reduced dose of intravesical BCG Increased time between treatments of intravesical BCG	Each other No intervention	Treatment-related toxicity Health-related quality of life inc. patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?
Patients select intravesical BCG or radiotherapy with the expectation of retaining their bladder. Treatment side effects can impact on quality of life to the extent that they then opt for cystectomy or long term catheterisation as a last resort.
Identification of methods to prevent long term side effects and / or effective treatments to manage their side effects could significantly improve patients' quality of life.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No date limits will be used

Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Comparative studies will be used unless no comparative evidence is available. Data will be extracted about the nature of bladder toxicity as stated in the included studies. Relevant study checklists will be used depending on study design (NICE Guideline Manual Appendices) Where appropriate data will be pooled and subgroups will include patient risk categories, type of treatment received, and disease status.

Note any changes to the protocol or other considerations below

Review protocol section 4.4: What is the optimum follow-up for patients with bladder cancer?

Clinical question section 4.4: What are the optimal follow-up protocols for low/intermediate risk and high-risk non-muscle invasive bladder cancer?

Rationale:
Please write a background in plain language explaining why we are asking the clinical question.
Include any relevant information that may help with reviewing the evidence such as:
Why is this topic contentious? Is there disagreement between healthcare professionals or variation in practice across the UK?
What are the benefits and harms of the alternative treatments or tests?
What kind of recommendations could you imagine yourself making following the evidence review?
Non-muscle invasive bladder cancer (NMIBC) frequently recurs but can also progress by growing deeper into or outside of the bladder wall. NMIBC can be divided into low, intermediate and high risk groups based on the risk of recurrence and progression.

Currently all patients with NMIBC require regular cystoscopic surveillance of their bladder and high risk patients may require additional imaging to look for progression. Long term cystoscopic surveillance is expensive and may not be necessary in low risk cases.

Although there is general agreement that NMIBC patients require cystoscopic surveillance to detect recurrence, there are variations in frequency and length of follow-up. The optimal tests for detecting progression are unknown. It is also difficult to co-ordinate current surveillance protocols with concurrent treatment e.g. with intravesical therapy.

Cystoscopic surveillance could be rationalised into low, intermediate and high risk group. Defining the optimal length of follow-up in low risk patients would allow many to be safely discharged whilst high risk patients would benefit from an integrated follow-up that is synchronised with treatment and includes imaging for progression.

Alternative approaches could include non invasive follow up using ultrasound for some risk groups and/or defining a group of patients in whom invasive surveillance may not be appropriate.

Patients with NMIBC are at increased risk of developing upper tract TCC. Tests to detect upper tracts tumour in these patients are variably performed at present but should be considered within follow up protocols

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients who have undergone curative treatment for NMIBC Subgroups: Low/intermediate-risk NMIBC High-risk NMIBC	Follow up: Cystoscopy intervals (rigid/flexi) Intravenous urography (IVU) CT Ultrasound Urine tests (Cytology, NMP22, UroVysion, ImmunoCyt)	No follow-up Each other (including frequency and duration of follow-up)	Recurrence Overall survival Disease progression Disease-specific survival Treatment related complications Health-related quality of life Patient experience

			Patient preference

Why are the outcomes listed in the above PICO important to patients?
Patients with NMIBC will have frequent cystoscopic examinations that are stressful and uncomfortable but are keen for recurrences or progression to be detected in a timely manner.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No
List useful search terms.	Non-muscle invasive bladder cancer, risk category, recurrence, cystoscopic surveillance

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Data will be extracted regarding the population, cancer stage/grade, and treatment received. The duration and frequency of follow-up protocols will be presented. Non-comparative data will be considered. Relevant quality checklists from the NICE guidelines manual will be used e.g. RCT and cohort study checklist. Subgroups including those listed in the PICO will be considered. It is unlikely that any meta-analysis will be suitable for this topic.

Note any changes to the protocol or other considerations below

Review Protocol for: section 5.1: What are the comparative patient outcomes for treating muscle invasive bladder cancer with: Neo-adjuvant and adjuvant chemotherapy

Clinical question section 5.1.1: Which patients with bladder cancer should be offered neoadjuvant chemotherapy?

Rationale:
Please write a background in plain language explaining why we are asking the clinical question.
Include any relevant information that may help with reviewing the evidence such as:
Why is this topic contentious? Is there disagreement between healthcare professionals or variation in practice across the UK?
What are the benefits and harms of the alternative treatments or tests?
What kind of recommendations could you imagine yourself making following the evidence review?

Newly diagnosed bladder cancer covers a wide spectrum of disease states. Many patients' tumours can be successfully treated by relatively simple operations which do not necessitate removal of the bladder. In particular, those tumours which have not invaded the muscle of the bladder wall can usually be treated in this way. However some of these tumours do require more major surgery, such as complete removal of the bladder (cystectomy). Furthermore, if the tumour has invaded the muscle of the bladder wall, then there is a very high risk that the patient will die of bladder cancer without either cystectomy or intensive radiotherapy. Although cystectomy or radiotherapy offers the best chance of cure, unfortunately a significant proportion of these patients still go on to die of bladder cancer. This is usually due to the cancer returning either in the region of the bladder or, more typically, in other parts of the body such as the lungs, lymph nodes, liver or bones. For many cancers this risk of relapse can be reduced or delayed by giving drug treatments such as chemotherapy before and / or after surgery / radiotherapy. Two large trials have demonstrated that some patients with bladder cancer which has invaded the muscle wall undergoing either cystectomy or radiotherapy have better outcomes if they receive prior chemotherapy. However, this treatment is associated with significant side effects. These side effects may be more problematic in patients with other illnesses or patients who are generally less fit. At worst, the occurrence of side effects may prevent the patient from undergoing successful surgery or radiotherapy. Therefore careful selection of patients for this treatment is essential, or there is a real risk of doing more harm than good.

During this review, consideration should be given to the following specific questions:
Which patients should be offered neoadjuvant chemotherapy?
What is the optimal type, schedule and duration of neoadjuvant chemotherapy?
Who should see the patient to make this this assessment? General urologist, urologist with an interest in bladder cancer, or oncologist?
What are the information needs of patients considering the offer of neoadjuvant chemotherapy and how are these best met?

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with MIBC undergoing radical treatment	Radical treatment alone Radical treatment plus neoadjuvant chemotherapy TURBT & neoadjuvant chemotherapy	Each other	Overall survival Disease-free survival Metastases free survival Treatment-related morbidity Treatment-related mortality Health-related quality of life,

			inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?
Most patients are prepared to undergo morbid treatment if there is realistic possibility of cure. Overall survival captures the reduction in death due to disease, but also any excess deaths caused by the treatment. Disease free survival is also important, as patients prefer to survive without the morbidity of recurrent or metastatic disease than with it. As these treatments all have significant side effects, it is important to consider these (morbidity and mortality). HRQoL encompasses the impact of relieving the burden of disease but also the negative impacts of these treatments.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	After existing systematic review (2003/2005)
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	RCT filter and meta-analysis should be considered.
List useful search terms.	Bladder; neo-adjuvant; peri-operative; adjuvant; chemotherapy

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Data will be extracted regarding the population, cancer stage/grade, and treatment. Where possible, RCT data will be pooled and effect size estimates will be presented. The RCT quality checklist in the NICE guidelines manual will be used. Evidence will be presented using GRADE. Meta-analysis of RCTs will be conducted where possible using RevMan. The chemotherapy regime will be an important consideration for the review.

Review Protocol for section 5.1.2: What are the comparative patient outcomes for treating muscle invasive bladder cancer with: Neo-adjuvant and adjuvant chemotherapy

Clinical question section 5.1.2: Which patients with bladder cancer should be offered adjuvant chemotherapy?

Muscle invasive bladder cancer (MIBC) is usually treated locally by radiotherapy and surgery. However the average 5 year survival for patients with MIBC is in the order of 50-60%. Patients dying of MIBC most commonly do so following the development of metastatic (cancer at distant sites) disease. It is,thus, logical to consider that to significantly improve the prognosis it will be necessary to reduce the incidence of the development of metastatic disease.

Chemotherapy induces responses in about 50% of patients with metastatic disease including about 10% of patients achieving complete response and prolongs survival but rarely, if ever, achieves long term cures. Metastatic relapse is thoughts to occur due to the presence of sub clinical metastatic deposits that subsequently progress. It is theorised that chemotherapy may be more likely to eradicate this metastatic disease when subclinical and thus reduce metastatic relapse and improve survival. Neo-adjuvant or adjuvant chemotherapy (chemotherapy given before [neo-adjuvant] or after [adjuvant] local treatment in patients with no clinically evident metastatic disease) has been shown to improve survival at a number of cancer sites (e.g. Breast cancer, Colorectal cancer).
A number of trials have been conducted in bladder cancer of both Neo-adjuvant and adjuvant chemotherapy that have been suggestive of benefit. Clinical implementation has been mixed. For example, studies in US have suggested <10-20% of MIBC are receiving (neo) adjuvant chemotherapy and there remains disagreements whether neo adjuvant or adjuvant therapy should be offered to all suitable patients or selected patients.

Thus, do these studies provide convincing evidence of survival benefit? If so is there evidence that any groups of patients benefit more than others or should treatment be offered to all patients with localised MIBC? Are there selection criteria or contra-indications for (neo)-adjuvant chemotherapy? Is there any evidence as to whether it better to use neo-adjuvant chemotherapy or use adjuvant chemotherapy for all or selected cases? What are the risk of this therapy? Do the risks outweigh benefit for some patients? Are there any recommendations on type of chemotherapy? Most studies have been cisplatin based? Can other chemotherapy such as carboplatin based therapy be used?

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with MIBC undergoing radical treatment	Radical treatment plus adjuvant chemotherapy	Radical treatment alone	Overall survival Disease-free survival Metastases free survival Treatment-related morbidity Treatment-related mortality Health-related quality of life, inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?

The main of such therapy to enhance the cure rates of patients and avoid need to relapse treatment. Overall, Disease free and metastatic survival are therefore key parameters. As a proportion of patients may be cured without this therapy it is also important to consider issues of treatment mordididty and impact on HRQOL

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	Search from after the existing 2005 meta analysis
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	Yes RCT and systematic review
List useful search terms.	Neo adjuvant, pre-emptive, adjuvant chemotherapy

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Data will be extracted regarding the population, cancer stage/grade, and treatment. Where possible, RCT data will be pooled and effect size estimates will be presented. The RCT quality checklist in the NICE guidelines manual will be used. Evidence will be presented using GRADE. Meta-analysis of RCTs will be conducted where possible using RevMan. The chemotherapy regime will be an important consideration for the review.

Note any changes to the protocol or other considerations below

Review Protocol for section 5.2: What are the comparative patient outcomes for treating muscle invasive bladder cancer with: Radical cystectomy with urinary stoma or bladder reconstruction, Radical radiotherapy (including a comparison of different radiotherapy schedules and chemoradiotherapy)

Clinical question 5.2.1: In which patient groups with muscle invasive bladder cancer would radical cystectomy produce better outcomes than radical radiotherapy and in which groups would radical radiotherapy produce better outcomes?

Rationale:
Please write a background in plain language explaining why we are asking the clinical question. Include any relevant information that may help with reviewing the evidence such as:
Why is this topic contentious? Is there disagreement between healthcare professionals or variation in practice across the UK?
What are the benefits and harms of the alternative treatments or tests?
What kind of recommendations could you imagine yourself making following the evidence review?

About a quarter of all bladder cancer patients have cancer in the muscle coat of the bladder (muscle invasive bladder cancer, or MIBC). This has a high risk of spread and presents an immediate threat to life. We know that when surgery is done to remove the bladder (cystectomy) because of MIBC, in about 20 to 25 % of patients, there is microscopic evidence of spread to the lymph glands at this stage, implying that the same level of risk of lymph gland involvement may be the case for all patients with MIBC. Spread to the lymph glands usually reduces the chance of cure sharply. This is the basis of the immediate threat in MIBC.

Although there is high quality evidence to support the use of intravenous chemotherapy as the initial treatment of MIBC for those patients who are able to manage it, there is no similar quality evidence to guide on which is the best local treatment for MIBC. Some form of local treatment is always recommended, because after telescopic removal of tumour (TURBT) with or without subsequent chemotherapy, the most likely site of remaining tumour is the bladder, and the site from which tumour is most likely to return, is the bladder.

The two treatment options are cystectomy and radiotherapy. We do not have high quality evidence to compare their benefits, so we do not know for sure which is the more effective treatment for MIBC. We do know that cystectomy has a far greater impact on patients than does radiotherapy, meaning a much harder treatment to cope with and a far higher likelihood of significant side-effects. In many countries at present, including the UK, there is a view that the chance of cure may be higher with cystectomy than radiotherapy, and this is the justification for the common recommendation of cystectomy rather than radiotherapy, despite the higher risk of side-effects.

There are believed to be some adverse factors for surgery and some adverse factors for radiotherapy. Being frail or elderly, having other serious medical conditions, or not having sufficient mental capacity to be able to participate actively in recovery from cystectomy are regarded as adverse factors for surgery. Some factors, conversely, are regarded as adverse for radiotherapy: these include previous pelvic radiotherapy, certain bowel disorders (inflammatory bowel disease), significant previous pelvic surgery (that might result in adhesions with bowel stuck to the bladder), and some factors related to the tumour, such as obstruction to one or both kidneys, or carcinoma in situ.

Given that the treatments differ so much in terms of their impact, it is crucial to identify those patients who would have better outcomes with surgery than with radiotherapy, and vice versa.

Recommendations for local treatment for MIBC are likely to address:
Which factors influence cancer outcomes from cystectomy and radiotherapy ?
Which factors influence side-effects from cystectomy and radiotherapy ?
Which patients will have better outcomes with cystectomy and which will have better outcomes with radiotherapy ?

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with diagnosed (non metastatic M-0) MIBC Subgroups: Performance status Patient age Gender Co morbid disease (renal failure) Previous treatment Tumour characteristics (Variant urothelial histology, non urothelial, presence of concomitant carcinoma in situ, T-stage, N-stage) Hydronephrosis	Radical cystectomy Radical radiotherapy (inc. Chemo-radiation) Radical cystectomy & Radical radiotherapy	Each other	Overall survival Disease-free survival Metastases free survival Treatment-related morbidity Treatment-related mortality Health-related quality of life inc, patient reported outcomes Subsequent treatment

Why are the outcomes listed in the above PICO important to patients?
Cancer outcomes are the most obvious outcome of relevance because successful treatment of the cancer is what the treatment is being given for.
HRQoL is a crucial outcome, because "the price" of successful cancer treatment is a fundamental part of the weighing up of treatment options that patients do

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No
List useful search terms.	Radical cystectomy Radical cystourethrectomy Salvage cystectomy Radical radiotherapy Radical chemoradiotherapy

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Data will be extracted regarding the population subgroups listed in the PICO. Where possible RCT data will be pooled and effect size estimates will be presented. The RCT quality checklist in the NICE guidelines manual will be used. Evidence will be presented using GRADE. Meta-analysis of RCTs will be conducted where possible using RevMan. Subgroups may include those listed in the PICO. The type of surgery and radiotherapy regime will also be important considerations for the review.

Note any changes to the protocol or other considerations below

After discussion with the GDG it was decided that studies of neoadjuvant RT+cystectomy versus cystectomy alone where patients were treated prior to 1990 should be excluded as RT and cystectomy have changed since then (so these studies are not relevant to current practice). Only comparative studies were selected at first, but it was considered relevant by the subgroup lead to also include large series (>100 patients) of combined multi-modality therapy and large recent cystectomy series (>1000 patients, comparable to UK practice).

Review Protocol for 5.2.2: What are the comparative patient outcomes for treating muscle invasive bladder cancer with: Radical cystectomy with urinary stoma or bladder, reconstruction, Radical radiotherapy (including a comparison of different radiotherapy schedules and chemoradiotherapy)

Clinical question section 5.2.2: What is the optimal radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer?

Rationale:
Muscle-invasive bladder cancer can be cured using external beam radiotherapy or surgery with 5 year survival rates of 50-60%. The two treatments have not been compared head-to-head in a randomised control trial. This question will be considered in topic H1. Within the UK, there is variation in radiotherapy schedules used to treat bladder cancer. The two most common schedules are 52.5-55 Gy in 20 fractions over 4 weeks and 64Gy in 32 fractions over 6.5 weeks. The two schedules have never been directly compared and to date, radiotherapy trials in the UK have included both regimes. The most common side effects during treatment are urinary frequency, discomfort, diarrhoea, nausea and tiredness. In the long term, there is a small risk of reduced bladder volume, continuing bowel symptoms, haematuria, loss of reproductive capacity, vaginal stenosis in women and impotence in men. Treatment side-effects and disease-outcome are considered to be comparable between the two protocols. Although many UK centres now treat potentially curative patients with radiotherapy and a radiosensitiser, there are a group of patients who are not fit or able to tolerate radiosensitisation. These patients are treated with radical radiotherapy alone as their definitive treatment.

When defining the volume of tissue receiving radiotherapy, some clinicians treat the bladder alone whereas, other clinicians include the pelvic lymph nodes within the treated volume for patients considered to be at high risk of bladder cancer spread within the nodes. There is no clear clinical advantage to treating a larger volume of tissue, however, side effects for the patient may be greater when treating the pelvic nodes compared to treating the bladder alone.

The addition of chemotherapy or hypoxic modifying agents have been tested in both phase II and III studies, and have found to improve clinical outcomes by 5-10% compared to radiotherapy alone. The improved clinical outcome may be associated with an increase in toxicity. A number of different agents have been used in combination with radiotherapy to increase radiosensivity. The most commonly used agents are mitomycin C and 5-Fluorouracil, carbogen and nicotinamide, gemcitabine and cisplatin. The two largest RCTs have been undertaken in the UK in the last ten years: BC2001 and BCON. BC2001 compared radiotherapy alone versus radiotherapy with mitomycin C and 5-Fluorouracil. BCON compared radiotherapy alone with radiotherapy and carbogen and nicotinamide. Alongside these studies, the UK also recruited to a multicentre phase II study with gemcitabine during radiotherapy. A smaller RCT was carried out in Canada in the 1990s using cisplatin as the radiosensitiser. However, the different radiosensitisers have not been directly compared with each other in the context of a randomised control trial. Variation exists within UK practice due to the differences in ease of delivery, cost and toxicity of the different regimes. The different radiotherapy/chemoradiotherapy regimes have resource implications and any differences in outcomes between the two regimes would be of importance. Some patients have to travel long distances for treatment.

This review should aim to establish the optimum radiotherapy and chemoradiotherapy regimes which benefit patients with muscle-invasive bladder cancer by exploring which doses and fractionation maximise clinical outcomes while minimising side-effects. If possible, the review should aim to define which patients are most suitable radiotherapy alone or radiotherapy with

radiosensitisation. A measure of impact on resource utilisation would be relevant.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients offered radical radiotherapy for bladder cancer	Chemoradiotherapy Hypoxic-sensitisation	Radical radiotherapy Various regimens (e.g. dose, duration of treatment)	Overall survival Disease-free survival Treatment-related morbidity Treatment-related mortality Health-related quality of life, inc patient reported outcomes Metastases free survival

Why are the outcomes listed in the above PICO important to patients?

Since there are two alternative treatments that may be equally effective for certain patients but not for others, survival and quality of life outcomes are particularly important.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	After 1990 due to changes in radiotherapy techniques – move to CT planning and 3D conformal radiotherapy.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	As explained in the text phase II regimes in use within the UK. Therefore, RCT and phase II.
List useful search terms.	Bladder preservation, radical radiotherapy/chemoradiotherapy/radiosensitisers/hypoxic modifiers. Acute and late toxicity

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results?	Data will be extracted regarding the population, cancer stage/grade, and treatment. Where possible, RCT data will be pooled and effect size estimates will be presented.
Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted).	The RCT quality checklist in the NICE guidelines manual will be used. Evidence will be presented using GRADE. Meta-analysis of RCTs will be conducted where possible using

List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	RevMan. The radiotherapy regime will be an important consideration for the review.

Review Protocol for section 5.2.3: What are the comparative patient outcomes for treating bladder cancer with: radical cystectomy with urinary stoma or bladder reconstruction?

Clinical question section 5.2.3: Is bladder reconstruction or urinary stoma the more effective method of urinary diversion?

Rationale:
After removal of the bladder for bladder cancer (cystectomy), drainage of urine has to be re-established. This can be done by using a segment of bowel taken out of circuit from the remaining bowel, re-joining the remaining bowel, and then connecting the tubes draining urine from the kidneys (the ureters) to some configuration of the bowel segment. This can be done either by formation of a urinary stoma (ileal conduit), with urine draining continually into an external bag, or by one or other form of urinary reconstruction, where a pouch is made from bowel, and is connected either to the waterpipe (urethra), as a bladder substitute, or to the skin of the abdominal wall, as a catheterisable reservoir (Mitrofanoff procedure). A bladder substitute allows urine to be held and passed in a more or less normal way, and a catheterisable reservoir is emptied by passage of a catheter around three to four times each day. Neither of these options involve an external bag.

Rehabilitation after this sort of surgery is much quicker with a stoma, and the majority of patients learn very quickly how to empty and change their bag, whereas learning how to use a bladder substitute or a catheterisable reservoir requires much more time and effort on the patient's part, with more follow-up visits.

The price of the more simple and straightforward rehabilitation with a stoma is the need for an external bag continually, and the presence of a piece of bowel at the skin surface, whereas bladder reconstruction leaves only a scar, and no bag. For patients with a bladder substitute, urine is held and passed in a more or less normal way.

The short and long term complication rate is the same with a stoma or a bladder substitute, but catheterisable reservoirs have a re-operation rate of around twice that the other two operations (50%). Bladder reconstruction requires reasonable kidney function (to deal with the effect of absorption of acid substances by the pouch), normal bowel function (no inflammatory bowel disease), and motivation and adequate mental capacity.

There is no evidence that either health-related outcomes or health-related quality of life differ significantly with any of these forms of urinary diversion, and the decision for patients is based on whether they are offered choice, and then which form of diversion fits with their own priorities. This decision is made, ideally, after discussion with a specialist urologist, and with a specialist nurse and with patients who have had this kind of surgery. This is probably not routine in cancer centres in England and Wales.

Recommendations regarding urinary diversion are likely to address:
What factors influence outcomes with different forms of urinary diversion ?
How best should patients come to a decision about which form of urinary diversion is most suited to them ?

Question in PICO format

Population	Intervention	Comparison	Outcomes

Patients having cystectomy for bladder cancer	Bladder reconstruction/replacement Ileal conduit Continent diversion	Each other	Treatment-related morbidity Treatment-related mortality Adverse events Patient satisfaction Health-related quality of life, inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?
Adverse effects may be very significant and require further surgery.
HRQoL is a crucial outcome, because "the price" of successful cancer treatment is a fundamental part of the weighing up of treatment options that patients do.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	See below (update of existing systematic review)
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Data will be extracted regarding the population, cancer stage/grade, and surgery received. If RCT or comparative data are available, data will be pooled and effect size estimates will be presented. The RCT or cohort study quality checklist in the NICE guidelines manual will be used as appropriate for the included studies. Evidence will be presented using GRADE. Meta-analysis of RCTs will be conducted where possible using RevMan.

Note any changes to the protocol or other considerations below
Systematic review identified - after correspondence with subgroup decision made to update the review but select RCTs only published since 2006/7 as any further observational studies are not likely to be useful in answering the review question. Also look for further recent QoL studies in the QoL search. JH 21.08.2013

Review protocol section 5.4: What is the optimum follow-up for patients with bladder cancer?

Clinical question section 5.4: What is the optimal follow-up protocol for muscle invasive bladder cancer?

Rationale:
Please write a background in plain language explaining why we are asking the clinical question. Include any relevant information that may help with reviewing the evidence such as:
Why is this topic contentious? Is there disagreement between healthcare professionals or variation in practice across the UK?
What are the benefits and harms of the alternative treatments or tests?
What kind of recommendations could you imagine yourself making following the evidence review?
Patients previously treated for muscle invasive bladder cancer are at high risk of recurrence. These may occur locally (~20%) and / or, most ominously, as distant metastases (50%). The majority of recurrences are ultimately fatal. The goal of any follow-up protocol is appropriate detection of recurrences such that treatment outcomes may be optimised.

Follow-up protocols should therefore define the type and frequency of tests necessary to diagnose recurrences. These include radiological imaging, urine tests and cystoscopy. There is variation in current follow-up protocols many of which are not evidence based. Patients who have had radical surgery, radical radiotherapy or non-curative treatment may require different follow-up protocols. In addition many patients develop symptomatic recurrences between follow-up visits and several studies have recently shown that there is no difference in overall survival between asymptomatic patients with recurrences found at follow-up and those presenting with symptomatic recurrence.

Nomograms have been developed to predict the risk of recurrence for an individual patient but these have not been widely validated. However, they may be useful in allowing a stratified approach to follow-up based on risk and site of recurrence and thus inform the type and frequency of follow-up tests.

Patients with treated bladder cancer are at increased risk of developing upper tract TCC. Tests to detect upper tracts tumour in these patients are variably performed at present but should be considered within follow up protocols.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with MIBC who have Received treatment aimed at cure Not received treatment aimed at cure	Urine tests (Cytology, NMP22, UroVysion, ImmunoCyt) Cystoscopy (Flexi/Rigid) CT scan abdomen and pelvis with plain chest radiograph CT scan chest abdomen and pelvis MRI scan abdomen and pelvis PET scan IVU	No follow-up Each other (including frequency and duration of follow-up)	Local recurrence rate Overall survival Disease progression Distant metastasis free survival Disease-specific survival Treatment related complications Health-related quality of life Patient experience Patient preference

	Renography Blood tests Renal function tests		

Why are the outcomes listed in the above PICO important to patients?

The benefits of detecting recurrences early is an important issue for patients. It is likely that early detection of recurrence maximises the outcome from therapeutic intervention. Maximising overall survival is a key objective for patients. Survival without recurrence, progression or metastasis is better than survival with these features and may be associated with improved overall survival.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	Very little literature in this area so no
List useful search terms.	Muscle invasive bladder cancer, follow-up, protocol, palliative,

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Data will be extracted regarding the population, cancer stage/grade, and treatment received. The duration and frequency of follow-up protocols will be presented. Non-comparative data will be considered. Relevant quality checklists from the NICE guidelines manual will be used e.g. RCT and cohort study checklist. Subgroups including those listed in the PICO will be considered. It is unlikely that any meta-analysis will be suitable for this topic.

Note any changes to the protocol or other considerations below

Review Protocol for section 6.1.1: What are the comparative patient outcomes for treating metastatic bladder cancer with:

First-line chemotherapy

Clinical question section 6.1.1: *What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?*

Rationale:

Most patients who die of bladder cancer will do so with metastatic disease. The main treatment used to prolong life and palliate/alleviate the symptoms is chemotherapy. Most studies report benefits in terms of response, symptom control and survival but this comes at the cost of significant treatment related toxicity. Though there are anecdotal reports of long term survivors these seem to be rare. Most clinicians use cisplatin based multiagent chemotherapy that is suitable for patients with normal renal function and good performance status. What evidence if there that the gains out way the toxicity? Does the treatment need to be cisplatin based or can less intensive therapy be used? Gemcitabine Cisplatin (GC) is widely used but is this best schedule in comparison to other schedules such as MVAC, CMV or accelerated MVAC. Does adding paclitaxel (GCP) improve results? Are there any other additional therapies that can be recommended. Carboplatin has a better toxicity profile (less sickness, fatigue, neuropathy but more myelosuppression) than cisplatin but there are concerns that carboplatin schedules such as gemcitabine carboplatin or carboplatin/methotrexate /Vinblastine or Vincristine are less active. Does the evidence support this view leaving cisplatin based schedules as the treatment of choice despite their added toxicity? Most commonly 6 cycles of chemotherapy are used. Is there evidence that more or less chemotherapy than this would be suitable?

Many patients are elderly and/or have impaired performance status and/or impaired renal (kidney) function. In these patients there have been questions as to whether patients benefit from chemotherapy. Is the evidence that chemotherapy improves outcomes compared to best supportive care? If so what is the preferred schedule? Should carboplatin based treatment be used? Should some patients be treated with split dose cisplatin schedules? Are there are 'platinum free' schedules that are suitable? Are there groups or sub groups of patients that should/should not be treated?

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with incurable locally advanced or metastatic bladder cancer Cisplatin fit (GFR >60 PS 0/1)	Chemotherapy agents for first-line chemotherapy (alone or in combination): Methotrexate, Vinblastine, Adriamycin, Cisplatin, Gemcitabine, Carboplatin Paclitaxel Docetaxel	Each other (Cisplatin vrs Non Cisplatin) No treatment	Overall survival Progression free survival Treatment-related mortality Treatment related morbidity Health-related quality of life, inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?

Metastatic bladder cancer is incurable. Prolonging life and improving quality of life with the minimum risk of treatment related toxicity would be relevant endpoints for patients.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE

	Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	Post 1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	RCT filter will be used
List useful search terms.	Chemotherapy, Bladder , Urothelial, transitional cell, individual drug names, MVAC, CMV, GemCarbo, GemCis,

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	The evidence table for intervention studies will be used (NICE Guideline Manual Appendix K) Cisplatin versus non cisplatin based chemotherapy will be compared in the evidence review. Quality checklists for RCTs (NICE manual Appendix D) and meta-analysis and systematic reviews (NICE manual Appendix C) will be used RCT data will be pooled when appropriate and risk ratios presented for the identified outcomes. Indirect comparisons maybe conducted if possible.

Note any changes to the protocol or other considerations below

Review Protocol for section 6.1.2: What are the comparative patient outcomes for treating metastatic bladder cancer with:
Second-line chemotherapy
Clinical question section 6.1.2: *What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?*

Rationale:
Ist line chemotherapy for metastatic disease is widely accepted as appropriate treatment for at least a proportion of patients.
Management of patients who progress on or relapse after 1st line treatment is much more controversial. Prognosis is poor with median survivals measured in a few months. There is a wide variety of practice in whether to offer 2nd line therapy to such patients. It is likely response rates are less; and toxicity may be higher thus questioning the clinical benefits of treatment. A key question is first therefore whether there is a role for further chemotherapy in some or all patients? If so can we identify the patients that are most likely to benefit and/or those in which chemotherapy is ineffective and treatment be avoided.
If patients are thought suitable for chemotherapy what form should this be? Should patients be re-challenged with initial chemotherapy or alternative combination regime (eg MVAC if Gemcitabine/cisplatin) was used first. One drug, Vinflunine, has a European license for this indication. Should this treatment be recommended? Are other alternatives likely to be as effective (eg Paclitaxel) even though not licensed? Are single drugs better or worse option than combination?

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with incurable locally advanced or metastatic bladder cancer that has progressed following first line chemotherapy	Chemotherapy agents for second-line chemotherapy (alone or in combination): Paclitaxel, Irinotecan, Bortezomib, Pemetrexed, Oxaliplatin, Ifosfamide, Lapatinib, Docetaxel, Gemcitabine, Topotecan, Carboplatin, Vinflunine, Gefitinib, Sorafenib, Sunitinib, MVAC (vinflunine for search)	Each other best supportive care	Overall survival Progression free survival Treatment-related mortality treatment related morbidity Health-related quality of life, inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?
In this settind Quality of life is likely to be key end point for patients with overall survival and treatment toxicity as secondary considerations

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline &

	Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	1980's
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No – lack of RCTs means that non comparative data may need to be reviewed We are aware of only one RCT in this setting
List useful search terms.	Chemotherapy, Bladder , Urothelial, transitional cell, individual drug names, MVAC, CMV, GemCarbo, GemCis, 2nd line, relapse

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	The evidence table for intervention studies will be used (NICE Guideline Manual Appendix K) Quality checklists for RCTs (NICE manual Appendix D) and meta-analysis and systematic reviews (NICE manual Appendix C) will be used RCT data will be pooled when appropriate and risk ratios presented for the identified outcomes. Indirect comparisons maybe conducted if possible.

Note any changes to the protocol or other considerations below

Review Protocol for section 6.2.1: What are the comparative patient outcomes for treating metastatic bladder cancer with: Radiotherapy

Clinical question section 6.2.1: What is the optimal pelvic radiotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

Rationale:
Radiotherapy can be used to help patients with symptoms of incurable bladder cancer. It is most commonly used to treat bleeding from the bladder or pain from the bladder cancer itself or sites of spread. Radiotherapy is also used to improve local control rates in patients with advanced pelvic disease. Treatment is usually given between 1 and 10 fractions as an outpatient. Side-effects are related to the area treated but are usually well-tolerated. For example, bladder radiotherapy can result in short term urinary frequency and discomfort or diarrhoea and nausea. These symptoms can be easily managed using appropriate medication. There is little evidence of differences in toxicity and outcome of patients of different gender or age. The total dose and fractionation of radiotherapy varies across the UK. Some clinicians deliver palliative radiotherapy at the time of diagnosis whilst others delay treatment until the patient becomes symptomatic. There have been a limited number of randomised control trials in this topic.

This review should establish the optimum radiotherapy regime which benefits patients with incurable bladder cancer by establishing which doses and fractionation maximise symptom control and local disease control rates. The timing of radiotherapy (immediate at the time of diagnosis or delayed until patient is symptomatic) should also be evaluated.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with incurable locally advanced or metastatic bladder cancer	Palliative pelvic radiotherapy	Dose/fractionation, timing to treat, duration of treatment	Overall survival Progression free survival Treatment-related mortality treatment related morbidity Symptom control (haematuria/pelvic pain/urinary frequency) Health-related quality of life, inc patient reported outcomes

Why are the outcomes listed in the above PICO important to patients?
Overall survival, health-related quality of life, progression-free survival

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e.

	Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No date limits will be used
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No RCT filter
List useful search terms.	Palliative radiotherapy, bladder cancer, pelvis, pain, haematuria, symptom control

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Comparative studies will be included unless no comparative evidence is available. Relevant study checklists will be used depending on study design (NICE Guideline Manual Appendices) Where appropriate data will be pooled and risk ratios will be calculated.

Note any changes to the protocol or other considerations below

Review Protocol for Review Protocol for section 6.2.2: What are the comparative patient outcomes for treating metastatic bladder cancer with: Management of urinary tract obstruction

Clinical question section 6.2.2: What is the best way to manage cancer related ureteric obstruction in patients with bladder cancer?

Rationale:
In patients with locally advanced bladder cancer, with or without metastases, the tumour can sometimes obstruct one or both ureters (The tubes connecting the kidneys to the bladder). If only one kidney is obstructed, the opposite kidney can usually maintain normal kidney function. Here the decision to intervene is often based on whether the patient has symptoms such as loin pain or whether optimal kidney function is essential e.g to enable safe administration of systemic chemotherapy. However if both kidneys are obstructed then urine cannot pass and the patient will develop kidney failure which if untreated is fatal. Fortunately this type of presentation is relatively uncommon. Historically these patients were often managed conservatively with no intervention and this is still one option. However the obstruction can be relieved either by a urologist inserting a stent (an internal plastic drainage tube) under general anaesthetic or by a radiologist inserting a nephrostomy (a plastic drainage tube which comes out through the skin and drains into an external bag).

There are no current guidelines or good quality randomised trials in this area and treatment is often based on opinion or local resources leading to widespread variations in practice across the UK.

Not treating the obstruction is uniformly fatal and in the last decade as a result of a greater public awareness of issues surrounding end of life care is often unacceptable to patients and their carers. The benefit of surgical insertion of a stent is that the patient does not have an external urine bag. It may also be possible to remove some of the obstructing tumour. However often the tumour very advanced making it impossible to identify the ureteric openings to insert the stent and the patient who is often very sick from kidney failure will have been exposed to the risks of an anaesthetic but with an unsuccessful outcome. Even with successful stenting the obstructing tumour can prevent adequate urine drainage necessitating subsequent nephrostomy drainage.

The benefit of a nephrostomy insertion is that the procedure can be carried out under light sedation, if necessary in a ward setting (e.g ITU) and improvement in kidney function is independent of the tumour obstruction further down the ureter. The main disadvantage is that if the patient's blood clotting is deranged as is often the case in kidney failure, then nephrostomy insertion is potentially dangerous due to the risks of causing internal bleeding. It also requires an experienced interventional radiologist which may not be available particularly out of hours or in a small DGH

The benefits and harms of doing nothing or intervention with either a stent or a nephrostomy should be outlined. Recommendations should also cover whether the obstruction affects one or both kidneys and, in the latter group, whether or not the patient has reached end of life care.

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with cancer related ureteric obstruction	Urinary stent Surgery - urinary diversion Percutaneous nephrostomy	Best supportive care Each other	Improvement of renal function Symptom relief Treatment related morbidity subsequent

			chemotherapy Subsequent cystectomy Health-related quality of life inc patient reported outcomes Overall survival

Why are the outcomes listed in the above PICO important to patients?
Improvements in renal function will lead to symptom relief. Both treatments have morbidity particularly if the treatment is unsuccessful. If successful, intervention may allow subsequent treatment with improvement in HR-QOL. Overall survival with and without intervention is important to allow patients to decide whether intervention is worthwhile.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No date limits will be used
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No
List useful search terms.	Locally advanced bladder cancer, metastatic bladder cancer, malignant ureteric obstruction, ureteric stenting, percutaneous nephrostomy

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Comparative studies will be included unless no comparative evidence is available. Relevant study checklists will be used depending on study design (NICE Guideline Manual Appendices) Improvement of renal function and symptom relief will be reported depending on measures used in the included studies

Note any changes to the protocol or other considerations below

Studies were also considered if they included patients with ureteric obstruction caused by malignancies other than primary bladder cancer. There must be at least 50 patients with malignant obstruction for studies to be included in the evidence review.

Review protocol section 6.2.3: What specific interventions are most effective for patients with intractable bleeding or bladder pain who are nearing the end of their life (for example, nerve block, opioids, palliative radiotherapy, urinary diversion)?

Clinical question section 6.2.3: What specific interventions are most effective for patients with incurable bladder cancer and intractable bleeding?

Rationale:
Please write a background in plain language explaining why we are asking the clinical question. Include any relevant information that may help with reviewing the evidence such as:
Why is this topic contentious? Is there disagreement between healthcare professionals or variation in practice across the UK?
What are the benefits and harms of the alternative treatments or tests?
What kind of recommendations could you imagine yourself making following the evidence review?
Intractable bleeding from the bladder is one of the most serious terminal complications for patients with bladder cancer because it is difficult to manage, it is frightening for the patient and their carers and almost certainly means that the patient will have to be admitted to hospital for management. Intractable bladder bleeding may occur before the patient is in a terminal phase but it may be the terminal event for bladder cancer patients. This means that they may die in hospital and certainly may lose precious hours and days that they would have rather spent at home with their family. Severe bleeding can arise from the bladder cancer itself, radiation cystitis, cyclophosphamide induced cystitis and severe infection complicating all of these. When irrigation of the bladder through a three-way catheter fail to stop the haematuria, a
life-threatening situation can develop. Blood transfusion may not keep pace with the rate of blood loss. Patients with massive uncontrollable haematuria are often elderly and already extremely frail.

This topic will need to distinguish between non-terminal and terminal intractable bleeding from the bladder. The following text will focus on bleeding at the end of life.

Although a patient may have hoped not to be admitted to hospital for terminal care, hospital may be the best place to manage this complication especially if the patient and their carers are unprepared that this may be a terminal complication. It is currently unclear whether the majority of hospices feel confident to manage patients with intractable bladder bleeding either as in-patients or at home. Hospice in-patient and home care teams do have experience in managing patients with other types of cancer, for example lung and head and neck cancers who die of sudden intractable bleeding when the tumour invades a bleed vessel.

In hospital, there is much that needs to be improved about the care of bladder cancer patients with terminal intractable bleeding from the bladder. Firstly, not all patients admitted to hospital will be admitted under the care of urologists, especially if they are admitted as an emergency as almost all will be. There may be significant delays in starting appropriate treatment. Patients should be referred to a urologist and also to a Palliative Care Team. Referral to an oncologist may be appropriate.

Not all patients will have had prior contact with a palliative care team or even will have contact during this admission. There are important communication issues: patients and their carers may not know that they are nearing the end of life, they may not have had an opportunity to express their hopes and desires for end of life care. Specifically, related to intractable bladder bleeding they may not know how this affects prognosis, or what treatment options are available. If the bleeding is considered by the medical team to be likely to be terminal discussions should take place not only about treatment options for the bleeding but other palliative care interventions including for pain, anxiety and psychological or spiritual distress.

In terms of treatments for intractable bleeding a range have been tried and these include:
Palliative radiotherapy
Palliative TURBT
Urinary diversion
Embolisation
Palliative chemotherapy
Tranexamic acid

Recommendations regarding intractable bladder bleeding at the end of life are likely to address:
Communication issues for the patient and their family and preparation that this could be a terminal event
What are the treatment options for the intractable bleeding
What are the other supportive care options for the patient with intractable bleeding
Options for place of care of patients with intractable bleeding: Hospital, hospice, home, nursing home
When patients are cared for outside hospital, primary care and community teams may need specialist support

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with locally advanced, metastatic bladder cancer or otherwise incurable with: Intractable bleeding	Palliative radiotherapy Palliative TURBT Urinary diversion Embolisation Palliative chemotherapy Tranexamic acid	Best supportive care Each other	Successful treatment of bleeding Requirement for transfusion Patient-reported distress Treatment-related mortality Treatment related morbidity Health-related quality of life, inc patient & carer reported outcomes

Why are the outcomes listed in the above PICO important to patients?

Intractable bleeding from the bladder is frightening, life threatening and creates great discomfort. It currently almost certainly means that a patient has to be admitted to hospital for management which may prevent a patient spending their last precious days at home with their family.
If the intractable bleeding can be treated it may not be a terminal event giving the patient extra months, weeks or days of life.
Treatment options may be limited by age.
If the bleeding is terminal then it is essential that this plus all appropriate supportive care is given to the patient according to their wishes.
Traumatic and poor quality end of life care can have adverse psychological and physical health impacts on bereaved relatives.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No because unlikely to be many studies
List useful search terms.	Intractable bleeding from bladder Palliation in patients with intractable bladder bleeding Intravesical alum irrigation; ' Intravesical formalin; ' Hydrostatic pressure; ' Embolization; ' Hyperbaric oxygen for radiation cystitis; ' Sodium pentosanpolysulphate for chronic gross haematuria; ' Intravesical PG for cyclophosphamide-induced haematuria.

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	Data will be extracted regarding the population, cancer stage/grade, and treatment received. Severity of bleeding will be an important consideration. Relevant quality checklists from the NICE guidelines manual will be used e.g. RCT and cohort study checklist. The definitions of best supportive care will be presented as reported in the included studies. Where possible, data will be pooled and effect estimates will be presented.

Note any changes to the protocol or other considerations below

Review protocol section 6.2.4: What specific interventions are most effective for patients with intractable bleeding or bladder pain who are nearing the end of their life (for example, nerve block, opioids, palliative radiotherapy, urinary diversion)?

Clinical question section 6.2.4: What specific interventions are most effective for patients with incurable bladder cancer and pelvic pain?

Rationale:
Please write a background in plain language explaining why we are asking the clinical question.
Include any relevant information that may help with reviewing the evidence such as:
Why is this topic contentious? Is there disagreement between healthcare professionals or variation in practice across the UK?
What are the benefits and harms of the alternative treatments or tests?
What kind of recommendations could you imagine yourself making following the evidence review?
Intractable pain is one of the most serious end of life complications for patients with bladder cancer because it is difficult to manage, it is frightening for the patient and their carers.

This topic will need to distinguish between non-terminal and terminal intractable pain. The following text will focus on pain at the end of life.

This review question will look primarily at medical interventions for the management of intractable pain but the location in which they are administered is also important to patients. Most patients do not want to die in hospital and would refer to die at home or in a hospice. A recent publication by the End of Life Care Intelligence Network showed that 51% of bladder cancer patients die in hospital compared with 46% for urological cancer patients as a whole.

In hospital, there is much that needs to be improved about the care of bladder cancer patients with terminal pain. Firstly, not all patients admitted to hospital will be admitted under the care of urologists, especially if they are admitted as an emergency as almost all will be. There may be significant delays in starting appropriate treatment.

Not all patients will have had prior contact with a palliative care team or even will have contact during this admission. There are important communication issues: patients and their carers may not know that they are nearing the end of life, they may not have had an opportunity to express their hopes and desires for end of life care. Specifically, related to intractable pain they may not know how this affects prognosis, or what treatment options are available. If the pain is considered by the medical team to be likely to be terminal discussions should take place not only about treatment options for the pain but other palliative care interventions including for pain, anxiety and psychological or spiritual distress. This should include preferred place of death

Recommendations regarding intractable pain at the end of life are likely to address:
Communication issues for the patient and their family and preparation that this could be a terminal event
What are the treatment options for the pain
What are the other supportive care options for the patient with pain
Options for place of care of patients with pain: Hospital, hospice, home, nursing home

Question in PICO format

Population	Intervention	Comparison	Outcomes
Patients with incurable cancer related pelvic pain excluding pain due to bone mets	Nerve block Palliative radiotherapy Chemotherapy for bladder cancer Specialist palliative care/Pain specialist	Best supportive care, inc opioids Each other	Patient-reported pain Treatment-related morbidity Health-related quality of life, inc patient & carer reported outcomes

Why are the outcomes listed in the above PICO important to patients?
Patients die only once and it is important to provide optimal care to control symptoms in accordance with their wishes which may include not only wishes about type of treatment but place of death too. Traumatic and poor quality end of life care can have adverse psychological and physical health impacts on bereaved relatives.

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	No
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No
List useful search terms.	Terminal pain in bladder cancer

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we include in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane	Data will be extracted regarding the population, cancer stage/grade, and treatment received. Severity of bladder pain will be an important consideration. Relevant quality checklists from the NICE guidelines manual will be used e.g. RCT and cohort study checklist. The definitions of best supportive care will be presented as reported in the included studies. Pain may also be measured in various ways by the included studies, which will be considered in the evidence review. Where possible, data will be pooled and effect estimates will be presented.

Collaboration handbook).	

Note any changes to the protocol or other considerations below

Appendix 2 Search Strategies

NATIONAL COLLABORATING CENTRE FOR CANCER

Bladder Cancer Clinical Guideline

Chapter 2 – Patient Centred Care **Literature search summary**

Topic A: The information and support needs of patients with bladder cancer, including:
A1: What are the causative and contributory factors that result in the comparatively low levels of reported patient satisfaction (c.f. the National Patient Satisfaction Surveys) for bladder cancer patients within the group of urological cancers?
A2: Which elements of the information and support provided by clinical nurse specialists (CNS)/key workers are most important for bladder cancer patients and/or their carers, at the various stages of the patient pathway?
A3: Which elements of specialist palliative care services are most important for bladder cancer patients and/or their carers during end-of-life care?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	970	30	16/07/2013
Premedline	July 15, 2013	91	6	16/07/2013
Embase	1974 -	962	47	17/07/2013
Cochrane Library	As per database	64	6	16/07/2013
Web of Science (SCI & SSCI)	1970 -	1237	40	17/07/2013
AMED	1985 -	16	2	16/07/2013
Psycinfo	1806 -	17	1	16/07/2013
Cinahl	1937 -	19	2	16/07/2013
PROMS database	As per database	22	17	16/07/2013

Total References retrieved (after de-duplication): 82

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	577	96	23/09/2013
Premedline	Sept 23, 2013	19	3	24/09/2013
Embase	1974 -	1320	196	24/09/2013
Cochrane Library	As per database	86	13	24/09/2013
Web of Science (SCI & SSCI)	1970 -	1867	82	24/09/2013
AMED	1985 -	10	4	18/09/2013
Psycinfo	1806 -	28	8	18/09/2013
Cinahl	1937 -	362	53	24/09/2013

Total References retrieved (after de-duplication): 297

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	637	50	22/07/2013
Premedline	July 19, 2013	34	0	22/07/2013
Embase	1974 -	1033	56	29/07/2013
Cochrane Library	As per database	52	8	22/07/2013
Web of Science (SCI & SSCI)	1970 -	1255	55	30/07/2013
AMED	1985 -	24	5	22/07/2013
Psycinfo	1806 -	3	1	22/07/2013
Cinahl	1937 -	22	4	29/07/2013

Total References retrieved (after de-duplication): 112

Medline search strategy *(This search strategy is adapted to each database)*

Topic A1

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 patient-centred$.tw.
11 "patient-reported outcom$".tw.
12 PROMS.tw.
13 Consumer Satisfaction/
14 exp Consumer Participation/
15 exp Personal Satisfaction/
16 exp Patient Participation/
17 exp Attitude to Health/
18 exp "Patient Acceptance of Health Care"/
19 Patient Compliance/
20 exp Patient Satisfaction/
21 ((client$ or patient$ or user$ or carer$ or consumer$ or customer$) adj2 (attitud$ or priorit$ or perception$ or preferen$ or expectation$ or choice$ or perspective$ or view$ or satisfact$ or opinion$ or concern$ or issue$)).tw.
22 "quality of life".tw.
23 or/10-22
24 9 and 23

Topic A2

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 Choice Behavior/
11 Decision Making/
12 Decision Support Techniques/
13 decision$.tw.
14 (choic$ or preference$).tw.
15 or/10-14
16 Patient Compliance/
17 Informed Consent/
18 Treatment Refusal/
19 exp Consumer Satisfaction/
20 exp Consumer Participation/
21 exp Health Education/
22 or/16-21
23 15 and 22
24 ((patient$ or consumer$) adj1 (decision$ or choice$ or prefer$ or participat$)).tw.

25 ((man or men) adj1 (decision$ or choice$ or prefer$ or participat$)).tw.
26 ((personal or interpersonal or individual) adj (decision$ or choice$ or prefer$ or participat$)).tw.
27 or/23-26
28 Pamphlets/
29 pamphlet$.tw.
30 (leaflet$ or diary or diaries or booklet$ or guidebook$).tw.
31 sheet$.tw.
32 Cues/
33 cue$.tw.
34 (prompt$ or coach$).tw.
35 (checklist$ or check list$).tw.
36 (written or write).tw.
37 question$.tw.
38 (card$ or helpcard$).tw.
39 (video$ or tape$ or cd$ or film$ or dvd$ or telephone$ or phone$ or computer$ or internet or electronic).tw.
40 *internet/
41 or/28-40
42 Communication/
43 communicat$.tw.
44 Patient Education/
45 ((patient$ or consumer$) adj3 (educat$ or skill$ or teach$ or train$ or coach$)).tw.
46 42 or 43
47 44 or 45
48 46 and 47
49 41 or 48
50 (preconsultation$ or pre-consultation$).tw.
51 Office Visits/
52 (office adj3 visit$).tw.
53 consult$.tw.
54 (medical adj3 interview$).tw.
55 waiting room$.tw.
56 scheduled appointment$.tw.
57 ((prior adj3 visit$) or previsit$).tw.
58 "Appointments and Schedules"/
59 or/50-58
60 49 and 59
61 (information adj3 need$).tw.
62 information material$.tw.
63 (patient$ adj3 information).tw.
64 (information adj3 web$1).tw.
65 (information adj3 print$).tw.
66 (information adj3 electronic$).tw.
67 or/61-66
68 60 or 67
69 27 or 68
70 9 and 69
71 nurs$.mp.
72 (key adj worker).tw.
73 CNS.tw.
74 Physician-Patient Relations/ or Hospital-Patient Relations/ or Nurse-Patient Relations/ or Professional-Patient Relations/
75 or/71-74
76 9 and 75
77 exp Psychotherapy/
78 exp Cognitive Therapy/
79 exp Counseling/
80 exp Self-Help Groups/
81 exp Social Support/
82 exp Hotlines/
83 exp Telephone/

84 exp Internet/
85 ((hot or help$ or tele$) adj line$).mp.
86 (internet or website$).mp.
87 ((cognit$ or group$ or psycho$) adj (therap$ or supp$ or session$)).mp.
88 ((self help$ or supp$ or counsel$) adj (group$ or session$)).mp.
89 or/77-88
90 9 and 89
91 76 or 90

Topic A3

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp Palliative Care/
11 exp Terminal Care/
12 exp Terminally Ill/
13 palliat$.mp.
14 (terminal$ and (care or caring or ill$)).mp.
15 ((advanced or end stage or terminal$) adj4 (disease$ or illness$ or cancer$ or malignan$)).mp.
16 (last year of life or LYOL or life's end or end of life).mp.
17 or/10-16
18 9 and 17

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	103	7	02/06/2014
Premedline (May 30, 2014)	81	5	02/06/2014
Embase	195	10	02/06/2014
Cochrane Library	13	0	02/06/2014
Cinahl	15	2	02/06/2014
Psychinfo	2	0	02/06/2014
AMED	0	0	02/06/2014
Web of Science (SCI & SSCI)	164	8	02/06/2014

Total References retrieved (after de-duplication): 25

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	73	3	02/06/2014
Premedline (May 30, 2014)	27	3	02/06/2014

Embase	345	11	02/06/2014
Cochrane Library	26	0	02/06/2014
Cinahl	0	0	02/06/2014
Psychinfo	4	0	02/06/2014
AMED	0	0	02/06/2014
Web of Science (SCI & SSCI)	342	9	02/06/2014

Total References retrieved (after de-duplication): 37

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	29	0	02/06/2014
Premedline (May 30, 2014)	44	0	02/06/2014
Embase	157	2	02/06/2014
Cochrane Library	10	0	02/06/2014
Cinahl	23	2	02/06/2014
Psychinfo	0	0	02/06/2014
AMED	0	0	02/06/2014
Web of Science (SCI & SSCI)	131	3	02/06/2014

Total References retrieved (after de-duplication): 38

Topic I: Does smoking cessation affect outcomes for patients with bladder cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	852	177	26/10/2012
Premedline	Oct 25, 2012	20	11	26/10/2012
Embase	1974 -	1064	219	31/10/2012
Cochrane Library	As per database	31	1	26/10/2012
Web of Science (SCI & SSCI)	1970 -	890	141	30/10/2012
Psychinfo	1806 -	9	3	26/10/2012
AMED	1985 -	0	0	26/10/2012

Total References retrieved (after de-duplication): 303

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 or/1-8
10 exp "Tobacco Use Cessation"/
11 exp Smoking Cessation/
12 Tobacco/ or exp "Tobacco Use Disorder"/
13 (smoking adj (cessation or ceas$ or intervention or withdrawal or quit$ or stop$)).tw.
14 exp Smoking/pc, th [Prevention & Control, Therapy]
15 or/10-14

16 9 and 15
17 smok$.m_titl.
18 9 and 17
19 16 or 18
20 exp Cohort Studies/
21 exp Mortality/
22 exp Morbidity/
23 natural history.ti,ab.
24 prognos$.ti,ab.
25 course.ti,ab.
26 predict$.ti,ab.
27 exp "Outcome Assessment (Health Care)"/
28 outcome$1.ti,ab.
29 (inception adj cohort$1).ti,ab.
30 Disease Progression/
31 exp Survival Analysis/
32 exp Prognosis/
33 or/20-32
34 smok$.tw.
35 9 and 33 and 34
36 19 or 35

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	195	13	02/06/2014
Premedline (May 30, 2014)	38	10	02/06/2014
Embase	527	36	02/06/2014
Cochrane Library	17	1	02/06/2014
Psychinfo	0	0	02/06/2014
AMED	0	0	02/06/2014
Cinahl	196	0 (after search de-dup)	02/06/2014
Web of Science (SCI & SSCI)	191	27	02/06/2014

Total References retrieved (after de-duplication): 49

NATIONAL COLLABORATING CENTRE FOR CANCER

Bladder Cancer Clinical Guideline

Chapter 3 – Diagnosis & Staging of Bladder Cancer Literature search summary

Topic B & C: What are the diagnostic accuracies of urine testing technologies for new and recurrent bladder cancer? What are the most effective endoscopic techniques for diagnosing bladder cancer (for example white light, blue light, narrow band cystoscopy)?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008 -	1038	381	22/10/2012
Premedline	Oct 19, 2012	90	43	22/10/2012
Embase	2008 -	1711	555	23/10/2012
Cochrane Library	2008 -	95	33	24/10/2012
Web of Science (SCI & SSCI)	2008 -	2087	482	01/11/2012

Total References retrieved (after de-duplication): 1045

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	345	25	20/12/2012
Premedline	Dec 19, 2012	9	5	20/12/2012
Embase	1974 -	105	75	20/12/2012
Cochrane Library	As per database	28	2	20/12/2012
Web of Science (SCI & SSCI)	1970 -	84	62	20/12/2012

Total References retrieved (after de-duplication): 90

Medline search strategy *(This search strategy is adapted to each database)*

Search 1

1 Urinary Bladder Neoplasms/
2 Hematuria/
3 (bladder adj3 (cancer$ or neoplasms$ or carci$)).tw.
4 (hematuria or haematuria).tw.
5 or/1-4
6 *Urinary Bladder Neoplasms/su [Surgery]
7 Cystectomy/
8 ((bladder adj3 resect$) or cystectomy or turbt).tw.
9 or/6-8
10 Cystoscopy/
11 cystoscop$.tw.
12 (photo dynamic$ or photodynamic$ or fluorescence$).tw.
13 10 or 11
14 12 and 13
15 hypericin.tw.
16 548-04-9.rn.
17 hexvix.tw.
18 hexaminolevulinate.tw.
19 106-60-5.rn.
20 5-ALA.tw.
21 5-aminolevulinic acid.tw.

22 5-aminolevulinic acid hexyl ester.tw,rn.
23 or/14-22
24 5 or 9
25 23 and 24
26 Tumor Markers, Biological/
27 ((tumo?r or biological or molecular or histolog$ or biochem$ or genetic$ or urine or disease) adj3 marker$).tw.
28 26 or 27
29 5 and 28
30 In Situ Hybridization, Fluorescence/
31 fluorescence in situ hybridization.tw.
32 urovysion.tw.
33 or/30-32
34 5 and 33
35 Nuclear Proteins/
36 (nuclear matrix protein 22 or nmp22).tw,rn.
37 35 or 36
38 5 and 37
39 Urine/cy [Cytology]
40 Cytodiagnosis/
41 Cell Count/
42 immunocyt$.mp. or ucyt$.tw.
43 or/39-42
44 5 and 43
45 or/25 or 29 or 34 or 38 or 44
46 (animals/ or nonhuman/) not humans/
47 45 not 46
48 (editorial or letter or comment or case reports).pt.
49 47 not 48
50 "Sensitivity and Specificity"/
51 ROC Curve/
52 "Predictive Value of Tests"/
53 False Positive Reactions/
54 False Negative Reactions/
55 du.fs.
56 sensitivity.tw.
57 distinguish$.tw.
58 differentiate.tw.
59 identif$.tw.
60 detect$.tw.
61 diagnos$.tw.
62 (predictive adj4 value$).tw.
63 accura$.tw.
64 comparison.tw.
65 or/50-64
66 49 and 65
67 exp Diagnostic Errors/
68 "Reproducibility of Results"/
69 Observer Variation/
70 Diagnosis, Differential/
71 Early Diagnosis/
72 (reliab$ or reproduc$).tw.
73 or/67-72
74 49 and 73
75 Prognosis/
76 (predict$ or prognosis or prognostic).tw.
77 75 or 76
78 49 and 77
79 25 or 66 or 74 or 78
80 limit 79 to ed=20080301-20121022

Search 2

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 (narrow adj band).tw.
11 NBI.tw.
12 NBIC.tw.
13 Cystoscopy/mt [Methods]
14 or/10-13
15 9 and 14

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Undertook an update of the following HTA Report from March 2008 onwards:
Mowatt, G. et al Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer. Health Technology Assessment 2010; 14 (4)
With an additional search on narrow-band imaging as not covered by the HTA - basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	464	60	05/06/2014
Premedline (Jun 4, 2014)	115	50	05/06/2014
Embase	1020	147	05/06/2014
Cochrane Library	19	2	05/06/2014
Web of Science (SCI & SSCI)	503	63	05/06/2014

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	72	18	05/06/2014
Premedline (Jun 4, 2014)	6	3	05/06/2014
Embase	79	29	05/06/2014
Cochrane Library	14	4	05/06/2014
Web of Science (SCI & SSCI)	29	9	05/06/2014

Total References retrieved (after de-duplication): 271

Topic F1 (a & b): Does the technique of transurethral surgery in new and recurrent bladder cancer influence outcomes? And does random biopsy affect outcomes in people with non-muscle invasive bladder cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1063	117	21/03/2013
Premedline	Mar 21, 2013	64	16	22/03/2013
Embase	1974 -	1465	197	25/03/2013
Cochrane Library	As per database	177	4	22/03/2013
Web of Science (SCI & SSCI)	1970 -	1125	102	26/03/2013

Total References retrieved (after de-duplication): 265

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 or/1-8
10 (TUR or TURBT or TURB).tw.
11 (transurethral adj3 (resect$ or surg$)).tw.
12 Urologic Surgical Procedures/
13 Urinary Bladder Neoplasms/su [Surgery]
14 or/10-13
15 9 and 14
16 (muscularis adj3 propria).tw.
17 (detrusor adj3 muscl$).tw.
18 (random adj3 biops$).tw.
19 ((exten$ or complete$ or enbloc or en-bloc or differentiat$) adj3 (resect$ or TURBT or TURB or TUR)).tw.
20 (quality adj3 (transurethral or resect$ or surg$ or TURBT or TURB or TUR)).tw.
21 or/16-20
22 9 and 21
23 14 and 21
24 22 or 23
25 limit 15 to systematic reviews
26 24 or 25
27 exp Clinical Competence/
28 9 and 27
29 14 and 27
30 26 or 28 or 29

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search

Medline (Pubmed checked)	136	5	02/06/2014
Premedline (May 20, 2014)	91	6	02/06/2014
Embase	309	33	02/06/2014
Cochrane Library	31	0	02/06/2014
Web of Science (SCI & SSCI)	134	11	02/06/2014

Total References retrieved (after de-duplication): 43

Topic D: What is the most effective imaging for staging newly diagnosed and recurrent bladder cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	2623	274	03/10/2013
Premedline	Oct 1, 2013	149	19	03/10/2013
Embase	1974 -	4536	440	08/10/2013
Cochrane Library	As per database	102	11	03/10/2013
Web of Science (SCI & SSCI)	1970 -	3995	208	09/10/2013

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	197	5	16/10/2013
Premedline	Oct 15, 2013	32	1	16/10/2013
Embase	1974 -	704	17	16/10/2013
Cochrane Library	As per database	9	0	16/10/2013
Web of Science (SCI & SSCI)	1970 -	1099	18	21/10/2013

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1228	214	06/09/2013
Premedline	Sept 5, 2013	29	2	06/09/2013
Embase	1974 -	3283	297	16/09/2013
Cochrane Library	As per database	50	6	09/09/2013
Web of Science (SCI & SSCI)	1970 -	4729	191	11/09/2013

Total References retrieved (after de-duplication): 937

Medline search strategy *(This search strategy is adapted to each database)*

Search 1

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 or/1-8
10 exp Urography/
11 (urograph$ or IVU or pyelograph$).tw.
12 10 or 11
13 9 and 12

14 exp Tomography, X-Ray Computed/
15 exp Tomography/
16 (comput$ adj1 tomogra$).tw.
17 ((CT or CAT) adj (scan$ or imaging or examination)).tw.
18 14 or 15 or 16 or 17
19 9 and 18
20 13 or 19

Search 2

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 or/1-8
10 radiography, thoracic/ or bronchography/
11 ((chest or thoracic) adj3 (radiograph$ or xray or x-ray)).mp.
12 (PET adj (scan$ or imag$ or examination)).tw.
13 positron emission tomograph$.mp.
14 PET$1.tw.
15 PET-CT.tw.
16 or/10-15
17 9 and 16

Search 3

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 or/1-8
10 exp Magnetic Resonance Imaging/
11 magnet$ resonance.mp.
12 (MRI or MRI$1 or NMR$1).tw.
13 (MR adj (imag$ or scan$)).tw.
14 (magnet$ adj (imag$ or scan$)).tw.
15 (magneti?ation adj3 imaging).tw.
16 or/10-15
17 9 and 16

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	122	5	04/06/2014
Premedline (3 Jun, 2014)	53	1	04/06/2014
Embase	666	35	04/06/2014
Cochrane Library	67	0	04/06/2014
Web of Science (SCI & SSCI)	423	15	04/06/2014

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	30	2	04/06/2014
Premedline (3 Jun, 2014)	38	1	04/06/2014
Embase	223	23	04/06/2014
Cochrane Library	5	1	04/06/2014
Web of Science (SCI & SSCI)	167	9	04/06/2014

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	77	1	04/06/2014
Premedline (3 Jun, 2014)	25	0	04/06/2014
Embase	661	27	04/06/2014
Cochrane Library	10	0	04/06/2014
Web of Science (SCI & SSCI)	495	16	04/06/2014

Total References retrieved (after de-duplication): 71

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Chapter 4 – Management of Non-Muscle Invasive Bladder Cancer — Literature search summary

Topic E: In addition to the factors specified in the EORTC risk tables, do TCC variants, differentiation of TCC and lymphovascular invasion predict recurrence and progression after treatment?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1456	387	04/03/2013
Premedline	Mar 1, 2013	104	42	04/03/2013
Embase	1974 -	1971	384	05/03/2013
Cochrane Library	As per database	53	9	06/03/2013
Web of Science (SCI & SSCI)	1970 -	2013	219	06/03/2013

Total References retrieved (after de-duplication): 648

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 or/1-8
10 predict.ti.
11 (validat* or rule*).ti,ab.
12 (predict* and (outcome* or risk* or model*)).ti,ab.
13 ((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
14 (decision* and (model* or clinical*)).ti,ab.
15 (prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
16 (stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
17 ROC Curve/
18 or/10-17
19 Models, Statistical/
20 decision*.ti,ab.
21 19 and 20
22 18 or 21
23 9 and 22
24 EORTC.tw.
25 "European Organization for Research and Treatment of Cancer".tw.
26 24 or 25
27 23 and 26
28 (EORTC adj3 (score$ or scoring or risk$ or model$ or rule$ or predict$ or validat$ or outcome$ or table$ or algorithm$ or nomogram$)).tw.
29 9 and 28

30 27 or 29
31 Lymphatic Metastasis/ or Lymph Nodes/
32 Lymphatic Vessels/
33 LVI.tw.
34 ((lymphovascular or lymphatic) adj3 invasion).tw.
35 or/31-34
36 23 and 35
37 33 or 34
38 9 and 37
39 36 or 38
40 Carcinoma, Papillary/
41 (micropapillary or MPC or MPUC or MPBC or MPV or IMC or IMPC).tw.
42 40 or 41
43 23 and 42
44 (micropapillary adj2 (variant$ or type$ or pattern$ or component$ or feature$)).tw.
45 9 and 44
46 43 or 45
47 (nest$ adj2 (variant$ or papillary or type$ or pattern$ or component$ or feature$)).tw.
48 9 and 47
49 squamous.tw.
50 glandular.tw.
51 sarcomatoid.tw.
52 ((TCC or transitional) adj2 (variant$ or differentiation)).tw.
53 or/49-52
54 23 and 53
55 30 or 39 or 46 or 48 or 54
56 limit 23 to systematic reviews
57 55 or 56

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	256	42	03/06/2014
Premedline (2 Jun, 2014)	125	41	03/06/2014
Embase	983	79	03/06/2014
Cochrane Library	8	2	03/06/2014
Web of Science (SCI & SSCI)	308	42	03/06/2014

Total References retrieved (after de-duplication): 148

Topic F2: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle invasive bladder cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1058	498	10/04/2013
Premedline	Apr 15, 2013	148	66	16/04/2013
Embase	1974 -	1485	555	16/04/2013
Cochrane Library	As per database	633	497	12/04/2013
Web of Science (SCI & SSCI)	1970 -	2571	452	15/04/2013

Total References retrieved (after de-duplication): 920

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 or/1-8
10 exp Mitomycin/
11 (mitomycin$ or mytomycin$ or mitomicin$ or mytomicin$).tw.
12 (mitosol or mutamycin).tw.
13 50-07-7.rn.
14 exp Epirubicin/
15 (epirubicin or ellence).tw.
16 56420-45-2.rn.
17 exp Doxorubicin/
18 (doxorubicin or adriamycin or rubex).tw.
19 23214-92-8.rn.
20 exp Deoxycytidine/
21 (gemc?tabin$ or Gemzar$).mp.
22 (gem?cis or gem?cisplat or gem?carbo).mp.
23 (gem adj (cis or cisplat or carbo)).mp.
24 exp Aziridines/
25 exp Indolequinones/
26 (EO9 or EO-9 or apaziquone or eoquin).tw.
27 114560-48-4.rn.
28 exp BCG Vaccine/
29 (bacillus calmette guerin or bcg).mp.
30 or/10-29
31 9 and 30
32 exp Administration, Intravesical/
33 intravesical drug administration/
34 (intraves$ or instill$ or region$ or install$).mp.
35 (induction or maintenance).tw.
36 or/32-35
36 31 and 35
37 9 and 35
38 36 or 37

2. Health Economics Literature search details

This topic was identified as an economic priority and further health economics work was undertaken but no additional searches were required. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter and Systematic Reviews and RCT filters were applied as an intervention topic. No date limits applied.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	80	14	03/06/2014
Premedline (2 Jun, 2014)	23	5	03/06/2014
Embase	155	35	03/06/2014
Cochrane Library	39	18	03/06/2014
Web of Science (SCI & SSCI)	274	32	03/06/2014

Total References retrieved (after de-duplication): 68

Topic F4: In patients with recurrent bladder cancer and previous low risk bladder cancer does treatment without histological sampling affect outcome?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000 -	1036	117	02/09/2013
Premedline	2000 -	212	11	03/09/2013
Embase	2000 -	1796	144	16/09/2013
Cochrane Library	As per database	515	23	04/09/2013
Web of Science (SCI & SSCI)	2000 -	1896	100	18/09/2013

Total References retrieved (after de-duplication): 254

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Urinary Bladder Neoplasms/
2. Ureteral Neoplasms/
3. ((bladder* or urethra* or ureter* or urin* or urotheli* or renal pelvis or calice*) adj3 (cancer* or carcinoma* or adenoma* or adenocarcinoma* or squamous or neoplas* or tumo?r* or malignan*)).tw.
4. exp Carcinoma, Transitional Cell/
5. ((recur* or progress*) adj3 ((bladder* or urethra* or ureter* or urin* or urotheli* or renal pelvis or calice*) adj3 (cancer* or carcinoma* or adenoma* or adenocarcinoma* or squamous or neoplas* or tumo?r* or malignan*))).tw.
6. or/1-5
7. (active adj1 surveillance).tw.
8. (active adj1 monitor*).tw.
9. watchful wait*.tw.
10. exp Watchful Waiting/
11. (watch* adj2 wait*).tw.
12. (watchful adj2 (observ* or surveillance or monitor*)).tw.
13. (expectant adj2 (surveillance or monitor* or treatment*)).tw.
14. ((defer* or delay*) adj2 (therap* or treatment*)).tw.
15. conservative monitoring.tw.
16. or/7-15

17. exp Cystoscopy/
18. cystoscop*.tw.
19. 17 or 18
20. (follow up or follow-up or followup or surveillance or monitor* or check).tw.
21. 19 and 20
22. (intravesical adj2 chemotherap*).tw.
23. (chemoresection or chemo-resection).tw.
24. 22 or 23
25. (fulguration or electrofulguration).tw.
26. exp Diathermy/
27. (diathermy or cystodiathermy).tw.
28. or/25-27
29. 16 or 21 or 24 or 28
30. 6 and 29

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	119	4	03/06/2014
Premedline (Jun 2, 2014)	133	3	03/06/2014
Embase	434	21	03/06/2014
Cochrane Library	56	2	08/04/2014
Web of Science (SCI & SSCI)	277	5	03/06/2014

Total References retrieved (after de-duplication): 26

Topic G1: Does re-resection in high risk NMIBC influence outcomes?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	509	95	27/11/2012
Premedline	Nov 26, 2012	33	13	27/11/2012
Embase	1974 -	760	185	28/11/2012
Cochrane Library	As per database	39	10	28/11/2012
Web of Science (SCI & SSCI)	1970 -	877	139	06/12/2012

Total References retrieved (after de-duplication): 257

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 reoperation/ or second-look surgery/
11 ((second$ or 2nd or subsequent$ or repeat$) adj2 (resect$ or TUR or TURB or TURBT)).tw.
12 (re-resect$ or reresect$ or re-TURB or re-TUR or re-TURBT or reTURB or reTUR or reTURBT).tw.
13 (sampl$ adj2 resect$).tw.
14 (re adj resect$).tw.
15 (restaging or re-staging).tw.
16 (re adj staging).tw
17 or/10-16
18 9 and 17
19 Neoplasm, Residual/
20 Neoplasm Staging/
21 19 or 20
22 resection.m_titl.
23 9 and 21 and 22
24 18 or 23

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	86	10	04/06/2014
Premedline (Jun 3, 2014)	43	6	04/06/2014
Embase	330	30	04/06/2014
Cochrane Library	7	0	04/06/2014
Web of Science (SCI & SSCI)	202	15	04/06/2014

Total References retrieved (after de-duplication): 34

Topic G2: For which patients with non-muscle invasive bladder cancer would primary cystectomy produce better outcomes than BCG?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	1946 -	1569	479	04/06/2014
Premedline	Apr 23, 2014	122	35	04/06/2014
Embase	1974 -	2730	525	04/06/2014
Cochrane Library	As per database	169	105	04/06/2014
Web of Science (SCI & SSCI)	1970 -	546 (focused search)	65	04/06/2014

Total References retrieved (after de-duplication): 810

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp Cystectomy/
11 cystectom$.tw.
12 10 or 11
13 BCG Vaccine/
14 BCG.tw.
15 "bacillus calmette-guerin".tw.
16 (intravesical adj3 (therap* or treatment)).tw.
17 or/13-16
18 exp Radiotherapy/
19 exp Radiation/
20 (radiation or irradiation or radiotherap*).tw.
21 exp Chemoradiotherapy/
22 (chemoradiotherap* or chemoradiation).tw.
23 or/18-22
24 9 and 17 and 23
25 9 and 12 and 17
26 24 or 25
27 ((early or earlier or defer* or delay* or immediate) adj3 cystectom*).tw.
28 Cystectomy/mt [Methods]
29 Time Factors/
30 9 and 28 and 29
31 9 and 33
32 26 or 30 or 31
33 (high-risk or high-grade or PT1G3 or T1G3 or T1).m_titl.
34 9 and 33
35 32 or 34
36 (conservative adj (management or treatment)).tw.
37 (bladder adj (sparing or conservation)).tw.
38 36 or 37
39 9 and 12 and 28

40 35 or 39

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

The figures for the update search have been combined with the initial search (see section 1 above).

Topic F3: What is the optimum treatment for patients with non-muscle invasive bladder cancer who have failed BCG?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1085	242	01/07/2013
Premedline	June 28, 2013	57	16	02/07/2013
Embase	1974 -	1853	280	05/07/2013
Cochrane Library	As per database	153	17	02/07/2013
Web of Science (SCI & SSCI)	1970 -	1223	155	11/07/2013

Total References retrieved (after de-duplication): 483

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 BCG Vaccine/
11 BCG.tw.
12 "bacillus calmette-guerin".tw.
13 or/10-12
14 ((BCG or bacill$ or calmett$ or guerin$) adj3 (refract$ or resistan$ or relaps$ or intoleran$ or contraindicat$ or naive or fail$)).tw.
15 (intravesical adj3 (refract$ or resistan$ or relaps$ or intoleran$ or contraindicat$ or naive or fail$)).tw.
16 14 or 15
17 9 and 16
18 exp Interferons/
19 (interferon$ adj2 (alpha$ or alfa$)).tw.
20 exp Cystectomy/
21 cystectom$.tw.
22 exp Chemoradiotherapy/
23 (chemoradiotherap$ or chemoradiation or chemoirradiation).tw.
24 exp Radiotherapy/
25 exp Radiation/

26 (radiotherap$ or radiation or irradiation).tw.
27 exp Mitomycin/
28 (mytomycin$ or mytomicin$ or mitomycin$ or mitomicin$ or mutamycin$ or mitosol).tw.
29 50-07-7.rn.
30 (gemcitabin$ or gemzar).mp.
31 B76N6SBZ8R.rn.
32 or/18-31
33 Paclitaxel/
34 (paclitaxel$ or docetaxel$).tw.
35 (taxol$ or taxotere$).tw.
36 33069-62-4.rn.
37 15H5577CQD.rn.
38 or/18-37
39 9 and 13 and 38
40 17 or 39
41 Hyperthermia, Induced/
42 hyperthermia.tw.
43 (thermochemotherap$ or thermo-chemotherap$ or chemohypertherm$).tw.
44 (electromotiv$ adj2 (administrat$ or instill$)).tw.
45 (EDMA or EMDA).tw.
46 or/41-45
47 9 and 46
48 40 or 47

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	85	8	03/06/2014
Premedline (2 Jun, 2014)	74	4	03/06/2014
Embase	324	16	03/06/2014
Cochrane Library	19	1	03/06/2014
Web of Science (SCI & SSCI)	145	12	03/06/2014

Total References retrieved (after de-duplication): 19

Topic M: What is the most effective intervention for bladder toxicity following radiotherapy or BCG therapy for bladder cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	475	50	16/11/12
Premedline	Nov 15, 2012	24	8	16/11/12
Embase	1974 -	951	205	14/11/12
Cochrane Library	As per database	169	14	20/11/12
Web of Science (SCI & SSCI)	1970 -	725	75	21/11/12
Biomed Central	As per database	35	2	20/11/12
Psychinfo	1806 -	0	0	16/11/12
AMED	1985 -	0	0	16/11/12

Total References retrieved (after de-duplication): 225

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	222	19	13/12/12
Premedline	Dec 13, 2012	2	1	13/12/12
Embase	1974 -	284	29	13/12/12
Cochrane Library	As per database	116	10	14/12/12
Web of Science (SCI & SSCI)	1970 -	203	60	18/12/12
Biomed Central	As per database	14	0	14/12/12
Psychinfo	1806 -	0	0	13/12/12
AMED	1985 -	0	0	13/12/12

Total References retrieved (after de-duplication): 80

Medline search strategy *(This search strategy is adapted to each database)*

1. exp urinary bladder neoplasms/
2. (bladder adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3. exp carcinoma, transitional cell/
4. (tcc or transitional cell).mp.
5. exp ureteral neoplasms/
6. bladder neoplasms/
7. urethral neoplasms/
8. ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous or neoplas$ or tumo?r$ or malignan$)).tw.
9. or/1-8
10. exp Drug Toxicity/
11. (toxic$ or failure or refractory or intoleran$ or resistan$).tw.
12. 10 or 11
13. BCG Vaccine/
14. (BCG or bacillus calmette guerin or calmette$ vaccin$ or oncotice or immucyst or calgevax or monovax or mycobax or pastimmun or ticebcg or tuberculosis vaccin$ or antituberculosis vaccin$ or theracys).tw.
15. 13 or 14
16. exp Radiotherapy/
17. (radiotherap$ or radiation therap$ or radiation treatment$ or irradiation).tw.
18. 16 or 17
19. 15 or 18
20. 12 and 19
21. 9 and 20
22. cystectomy/
23. (cystectom$ or excision or resection$ or extirpation$ or cystoprostatectom$).tw.

24. 22 or 23
25. exp Urinary Catheterization/
26. catheri?ation$.tw.
27. 25 or 26
28. exp Cholinergic Antagonists/
29. (anticholinergic$ or anti-cholinergic$ or cholinergic blocking or cholinergic antagonist$ or cholinolytic$ or acetylcholine antagonist$).tw.
30. (Darifenacin or Flavoxate or Oxybutynin or Propiverine or Solifenacin or Tolterodine or Trospium or Propantheline).tw.
31. or/28-30
32. Pentosan Sulfuric Polyester/
33. (pentosan$ polysulf$ or pentosanpolysulf$ or elmiron or thrombocid or xylan sulfate or pz68 or fibrocid or sp54 or polypentose sulfate or polysulf$ xylan or sulf$ xylan or hemoclar).tw.
34. 32 or 33
35. hyaluronic acid/
36. (hyaluronic acid or sodium hyaluron$ or biolon or cystistat or duralone or hyalgan or hyvisc or etamucine or amvisc or healon or luronit or hyaluronan or amo vitrax).tw.
37. 35 or 36
38. Ofloxacin/
39. (ofloxacin$ or tarivid or levaquin or quixin or levofloxacin).tw.
40. 38 or 39
41. Isoniazid/
42. (isoniazid$ or phthivazide or hydrazide isonicotinic acid or tubazide or isonex or ftivazide).tw.
43. 41 or 42
44. 24 or 27 or 31 or 34 or 37 or 40 or 43
45. 21 and 44

Additional Search

1. exp urinary bladder neoplasms/
2. (bladder adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3. exp carcinoma, transitional cell/
4. (tcc or transitional cell).mp.
5. exp ureteral neoplasms/
6. bladder neoplasms/
7. urethral neoplasms/
8. ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous or neoplas$ or tumo?r$ or malignan$)).tw.
9. or/1-8
10. exp Botulinum Toxins/
11. botulin$ toxin$.tw.
12. botox$.tw.
13. dysport$.tw.
14. exp Clostridium botulinum/
15. clostridium botulin$.tw.
16. or/10-15
17. exp Formaldehyde/
18. (formaldehyde or formalin).mp. or formol.tw.
19. 17 or 18
20. Hyperbaric Oxygenation/
21. Hyperbaric oxygen therapy.mp.
22. HBO.mp. or HBOT.tw.
23. or/20-23
24. exp Embolization, Therapeutic/
25. emboli?ation.mp.
26. 24 or 25
27. exp aluminum compounds/ or alum compounds/
28. alum.tw.
29. 27 or 28
30. 16 or 19 or 23 or 26 or 29

31. 9 and 30
32. exp Drug Toxicity/
33. (toxic$ or failure or refractory or intoleran$ or resistan$).tw.
34. BCG Vaccine/
35. (BCG or bacillus calmette guerin or calmette$ vaccin$ or oncotice or immucyst or calgevax or monovax or mycobax or pastimmun or ticebcg or tuberculosis vaccin$ or antituberculosis vaccin$ or theracys).tw.
36. exp Radiotherapy/
37. (radiotherap$ or radiation therap$ or radiation treatment$ or irradiation).tw.
38. or/34-37
39. 32 or 33
40. 31 and 38 and 39
41. exp BCG Vaccine/ad, ae [Administration & Dosage, Adverse Effects]
42. 9 and 41
43. 39 and 42
44. 40 or 43

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	82	3	03/06/2014
Premedline (Jun 2, 2014)	38	0	03/06/2014
Embase	305	6	03/06/2014
Cochrane Library	18	3	03/06/2014
Psychinfo	0	0	03/06/2014
AMED	0	0	03/06/2014
Cinahl	0	0	03/06/2014
Web of Science (SCI & SSCI)	80	13	03/06/2014

Total References retrieved (after de-duplication): 21

Topic K1 & K2: What are the optimum follow-up protocols for low-risk and high-risk non-muscle invasive bladder cancer? What is the optimum follow-up protocol for muscle invasive bladder cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	713	298	16/11/2012
Premedline	Nov 14, 2012	32	22	16/11/2012
Embase	1974 -	1032	422	19/11/2012
Cochrane Library	As per database	59	25	16/11/2012
Web of Science (SCI & SSCI)	1970 -	1151	329	16/11/2012
Psychinfo	1806 -	2	0	16/11/2012
AMED	1985 -	7	0	16/11/2012

Total References retrieved (after de-duplication): 518

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp Aftercare/
11 (aftercare or after-care or followup or follow-up or surveillance).m_titl.
12 ((post-treatment or posttreatment) adj1 evaluation$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13 ((post-treatment or posttreatment) adj1 care).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14 ((post-treatment or posttreatment) adj1 monitoring).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15 or/10-14
16 9 and 15

2. Health Economics Literature search details

This topic was identified as an economic priority and further health economics work was undertaken but no additional searches were required. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	75	17	02/06/2014
Premedline (30 May, 2014)	39	10	02/06/2014
Embase	246	56	02/06/2014
Cochrane Library	15	3	02/06/2014
Cinahl	168	0 (after search de-dup)	02/06/2014
Psychinfo	2	1	02/06/2014
AMED	0	0	02/06/2014
Web of Science (SCI & SSCI)	226	34	02/06/2014

Total References retrieved (after de-duplication): 70

NATIONAL COLLABORATING CENTRE FOR CANCER

Bladder Cancer Clinical Guideline

Chapter 5 – Management of Muscle-Invasive Bladder Cancer — Literature search summary

Topic H3 & H4: Which patients with bladder cancer should be offered neoadjuvant chemotherapy? Which patients with bladder cancer should be offered adjuvant chemotherapy?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2004 -	1330	184	18/03/2013
Premedline	2004 -	351	39	18/03/2013
Embase	2004 -	1353	168	18/03/2013
Cochrane Library	2004 -	126	25	18/03/2013
Web of Science (SCI & SSCI)	2004 -	667	174	18/03/2013

Total References retrieved (after de-duplication): 412

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Urinary Bladder Neoplasms/
2. (bladder adj3 (cancer* or carcinoma* or neoplas* or tumo?r*)).tw.
3. exp Carcinoma, Transitional Cell/
4. (invasive* adj bladder*).tw.
5. MIBC*.tw.
6. exp Urethral Neoplasms/
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Antineoplastic Combined Chemotherapy Protocols/
9. exp Chemotherapy, Adjuvant/
10. exp Cisplatin/
11. exp Cystectomy/
12. exp Doxorubicin/
13. exp Methotrexate/
14. exp Neoadjuvant Therapy/
15. exp Deoxycytidine/
16. Chemotherap*.tw.
17. adjuvant chemotherapy*.tw.
18. exp Radiotherapy, Adjuvant/
19. adjuvant radiotherap*.tw.
20. neoadjuvant* chemotherapy*.tw.
21. induction* chemotherapy*.tw.
22. perioperative* chemotherapy*.tw.
23. preoperative* chemotherapy*.tw.
24. Cystectomy*.tw.
25. surgery*.tw.
26. exp Drug Therapy/
27. or/8- 26
28. 7 and 27
29. limit 28 to yr="2004 -Current"

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter and Systematic Reviews and RCT filters were applied. Search was executed from 2004 onwards as per GDG decision, because of Cochrane reviews published in 2005.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	184	26	02/06/2014
Premedline	426	51	02/06/2014
Embase	231	21	02/06/2014
Cochrane Library	32	6	02/06/2014
Web of Science (SCI & SSCI)	167	31	02/06/2014

Total References retrieved (after de-duplication): 113

Topic H1: In which patient groups with muscle invasive bladder cancer would radical cystectomy produce better outcomes than radical radiotherapy and in which groups would radical radiotherapy produce better outcomes?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	2491	768	11/06/2013
Premedline	June 13, 2013	71	27	14/06/2013
Embase	1974 -	2870	668	13/06/2013
Cochrane Library	As per database	504	152	04/06/2013
Web of Science (SCI & SSCI)	1970 -	596 (focused)	189	22/10/2013

Total References retrieved (after de-duplication): 1210

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp Cystectomy/
11 cystectom$.tw.
12 exp Radiotherapy/
13 exp Radiation/
14 exp Chemoradiotherapy/
15 (radiation or irradiation or radiotherap$).tw.
16 (chemoradiotherap$ or chemoradiation).tw.

17 10 or 11 or 12 or 13 or 14 or 15 or 16
18 9 and 17
19 ((radical or total) adj (cystectom$ or radiotherap$ or radiation or irradiation or chemoradiotherap$ or chemoradiation)).tw.
20 9 and 19
21 18 or 20

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

The following Cochrane Review was a useful starting point for this topic:
Shelley M, Barber J, Wilt TJ, Mason M. Surgery versus radiotherapy for muscle invasive bladder cancer. Cochrane Database of Systematic Reviews 2001, Issue 4. Art. No.: CD002079. DOI: 10.1002/14651858.CD002079
Basic exclusions filter and then Systematic Reviews and RCT filters were applied for line 18 (2010 onwards), and observational studies filter (2001 onwards updating Cochrane Review). Then basic exclusions filter and then Systematic Reviews, RCT and observational filters were applied for line 19 (2001 onwards updating Cochrane Review). The GDG did not want to restrict the search to RCTs only, but the search was too large to do full search without filters or date limits, so the search strategy incorporated the terms 'radical' or 'total' in order to limit the results and also used the Cochrane Review above to restrict the date coverage.

4. Update Search

For the update search, an RCT filter was applied with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	67	12	04/06/2014
Premedline (Jun 3, 2014)	19	4	04/06/2014
Embase	349	25	04/06/2014
Cochrane Library	39	7	04/06/2014
Web of Science (SCI & SSCI)	65	16	04/06/2014

Total References retrieved (after de-duplication): 42

Topic H2: What is the optimal radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1990 -	771	271	19/06/2013
Premedline	June 17, 2013	40	19	18/06/2013
Embase	1990 -	1354	456	25/06/2013
Cochrane Library	As per database	91	34	20/06/2013
Web of Science (SCI & SSCI)	1990 -	760	268	21/06/2013

Total References retrieved (after de-duplication): 581

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp Radiotherapy/
11 exp Radiation/
12 (radiotherap$ or radiation or irradiation).tw.
13 or/10-12
14 9 and 13
15 exp Radiation-Sensitizing Agents/
16 Radiation Tolerance/
17 radiosensiti$.tw.
18 ((radiotherap$ or radiation or irradiation) adj3 (sensiti$ or toleran$ or resistan$)).tw.
19 (radiosensiti$ or radioresistan$).tw.
20 hypoxi$.tw.
21 or/15-20
22 exp Chemoradiotherapy/
23 (chemoradiotherap$ or chemoradiation or chemoirradiation).tw.
24 22 or 23
25 exp Mitomycin/
26 (mytomycin$ or mytomicin$ or mitomycin$ or mitomicin$ or mutamycin$ or mitosol).tw.
27 exp Fluorouracil/
28 fluorouracil$.tw.
29 flourouracil$.tw.
30 5FU$.tw.
31 5 FU$.tw.
32 (gemcitabin$ or gemzar).mp.
33 exp Cisplatin/
34 (cisplatin$ or cis-platin$ or platinol$ or cis-DDP or cis-diamminedichloroplatinum or DDP).tw.
35 50-07-7.rn.
36 51-21-8.rn.
37 103882-84-4.rn.
38 15663-27-1.rn.
39 or/25-38
40 (carbogen$ or nicotinamid$).tw.
41 exp Carbon Dioxide/
42 exp Oxygen/
43 exp Niacinamide/
44 or/40-43
45 14 and 39
46 14 and 44
47 14 and 21
48 9 and 24
49 or/45-48
50 limit 49 to yr="1990 -Current"

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only. Search was executed from 1990 onwards as per GDG decision due to changes in techniques in this area. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	72	13	04/06/2014
Premedline (3 Jun, 2014)	51	10	04/06/2014
Embase	223	45	04/06/2014
Cochrane Library	18	2	04/06/2014
Web of Science (SCI & SSCI)	84	22	04/06/2014

Total References retrieved (after de-duplication): 54

Topic H5: Is bladder reconstruction or urinary stoma the more effective method of urinary diversion?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2006 -	52	27	12/07/2013
Premedline	July 1, 2013	63	19	12/07/2013
Embase	2006 -	140	42	12/07/2013
Cochrane Library	As per database	68	31	12/07/2013
Web of Science (SCI & SSCI)	2006 -	372	103	12/07/2013

Total References retrieved (after de-duplication): 173

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	80	80	11/07/2013
Premedline	July 10, 2013	9	9	11/07/2013
Embase	1974 -	336	336	11/07/2013
Cochrane Library	As per database	29	29	11/07/2013
Web of Science (SCI & SSCI)	1970 -	297	297	11/07/2013
AMED	1970 -	8	1	11/07/2013
Pscyinfo	1806 -	9	4	11/07/2013

Total References retrieved (after de-duplication): 622 (QoL search – mainly unsifted)

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp Urinary Diversion/

11 Urinary Reservoirs, Continent/
12 Urinary Catheterization/
13 (conduit$ adj5 (ile$ or urin$ or contine$ or colon$)).tw.
14 ((continen$ or incontinen$ or urin$) adj2 diversion$).tw.
15 (reservoir$ adj5 (ile$ or urin$ or contine$ or colon$)).tw.
16 (bladder$ adj2 (substitut$ or reconstruc$ or artificial or replac$)).tw.
17 neobladder$.tw.
18 (cystoplast$ or enterocystoplast$).tw.
19 (continen$ adj2 outlet$).tw.
20 (conduit$ adj2 diversion$).tw.
21 (urin$ adj2 stoma$).tw.
22 mitrofanoff.tw.
23 urostom$.tw.
24 (urostom$ or cystostom$ or ureterostom$).tw.
25 or/10-24
26 9 and 25

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter and Systematic Reviews and RCT filters were applied. Search was executed from 2006 onwards due to systematic reviews on this topic. Quality of Life search also executed for whole guideline using ScHARR QoL search filter and no date limits.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	20	0	04/06/2014
Premedline (Jun 3, 2014)	22	4	04/06/2014
Embase	51	2	04/06/2014
Cochrane Library	21	0	04/06/2014
Web of Science (SCI & SSCI)	263	37	04/06/2014

Total References retrieved (after de-duplication): 47

Database name	No of references found	No of references retrieved	Finish date of search
Medline	13	4	04/06/2014
Pubmed	53	53	04/06/2014
Premedline (Jun 3, 2014)	11	7	04/06/2014
Embase	96	76	04/06/2014
Cochrane Library	14	0	04/06/2014
Web of Science (SCI & SSCI)	45	40	04/06/2014
AMED	0	0	04/06/2014
Psycinfo	1	0	04/06/2014
Cinahl	108	78	04/06/2014

Total References retrieved (after de-duplication): 235 (QoL search – mainly unsifted)

NATIONAL COLLABORATING CENTRE FOR CANCER

Bladder Cancer Clinical Guideline

Chapter 6 – Management of Patients with Advanced Bladder Cancer **Literature search summary**

Topic J1 & J2: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1013	287	10/01/2013
Premedline	Jan 9, 2013	8	3	10/01/2013
Embase	1974 -	1905	383	15/01/2013
Cochrane Library	As per database	398	120	15/01/2013
Web of Science (SCI & SSCI)	1970 -	1422	287	15/01/2013

Total References retrieved (after de-duplication): 605

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	118	31	28/01/2013
Premedline	Jan 25, 2013	13	3	28/01/2013
Embase	1974 -	454	106	28/01/2013
Cochrane Library	As per database	17	6	28/01/2013
Web of Science (SCI & SSCI)	1970 -	772	108	28/01/2013

Total References retrieved (after de-duplication): 157

Medline search strategy *(This search strategy is adapted to each database)*

Search 1

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 or/1-8
10 Paclitaxel/
11 (paclitaxel* or docetaxel*).mp.
12 (taxol* or taxotere* or abraxane).mp.
13 33069-62-4.rn.
14 114977-28-5.rn.
15 Methotrexate/
16 (methotrexate or methotrex$ or amethopterin or methotrexate hydrate or dicesium salt methotrexate or mexate or sodium salt methotrexate or disodium salt methotrexate or MTX or amethopter$ or mexat$ or MVAC).mp.
17 (Rheumatrex or Trexall).mp.
18 59-05-2.rn.

19 Carboplatin/
20 (carboplatin* or paraplatin* or CBDCA).mp.
21 Cisplatin/
22 (Cisplatin or cis-Diamminedichloroplatinum or Platinum Diamminodichloride or Diamminodichloride, Platinum or cis-Platinum or cis Platinum or Cisplatinum or Dichlorodiammineplatinum or cis-Diamminedichloroplatinum or cis Diamminedichloroplatinum or cis-Dichlorodiammineplatinum or Platinol or Platidiam or Platino or NSC-119875 or Biocisplatinum).mp.
23 15663-27-1.rn.
24 41575-94-4.rn.
25 Vinblastine/
26 (vinblastin* or velban).mp.
27 865-21-4.rn.
28 (gemcitabin$ or gemzar).mp.
29 103882-84-4.rn.
30 Doxorubicin/
31 (doxorubicin or adriamycin).mp.
32 23214-92-8.rn.
33 or/10-32
34 9 and 33
35 (first adj2 chemo*).m_titl.
36 9 and 35
37 34 or 36

Search 2

1 exp Urinary Bladder Neoplasms/
2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3 (tcc or transitional cell).mp.
4 exp Ureteral Neoplasms/
5 bladder neoplasms/
6 Urethral Neoplasms/
7 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8 exp Carcinoma, Transitional Cell/
9 or/1-8
10 (Irinotecan or Camptosar or camptothecin-11 or CPT-11 or SN-38).tw.
11 "7673326042".rn.
12 (bortezomib or velcade).tw.
13 (pemetrexed or alimta).tw.
14 04Q9AIZ7NO.rn.
15 (oxaliplatin or eloxatin).tw.
16 63121-00-6.rn.
17 Ifosfamide/
18 (ifosfamide or iphosphamide or iso-endoxan or iso endoxan or isophosphamide or isofosfamide or holoxan or asta z 4942 or NSC-109,724 or NSC 109,724 or NSC109,724 or NSC 109724 or NSC-109724 or NSC109724 or cyclic p-oxides or ethylamines or oxazines or ifosfa* or iphospha* or isofosfa* or isophospha* or Ifex).tw.
19 3778-73-2.rn.
20 Topotecan/
21 (topotecan or Hycamtin).tw.
22 123948-87-8.rn.
23 (gefitinib or ZD1839 or ZD 1839).mp.
24 Iressa.ti,ab.
25 184475-35-2.rn.
26 (sorafenib or nexavar).tw.
27 (sunitinib or sutent).tw.
28 (lapatinib or tykerb).mp.
29 0VUA21238F.rn.
30 or/10-29
31 9 and 30

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter and Systematic Reviews and RCT filters were applied as an intervention topic. No date limits applied.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	51	10	04/06/2014
Premedline (Jun 3, 2014)	17	3	04/06/2014
Embase	216	20	04/06/2014
Cochrane Library	52	9	04/06/2014
Web of Science (SCI & SSCI)	132	37	04/06/2014

Total References retrieved (after de-duplication): 58

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	8	2	04/06/2014
Premedline (Jun 3, 2014)	21	2	04/06/2014
Embase	59	6	04/06/2014
Cochrane Library	7	2	04/06/2014
Web of Science (SCI & SSCI)	92	12	04/06/2014

Total References retrieved (after de-duplication): 64

Topic J3: What is the optimal pelvic radiotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1331	393	19/07/2013
Premedline	July, 2013	128	17	19/07/2013
Psychinfo	1806 -	8	1	19/07/2013
Embase	1974 -	2543	681	08/08/2013
Cochrane Library	As per database	279	36	16/07/2013
Web of Science (SCI & SSCI)	1970 -	3352	398	23/08/2013

Total References retrieved (after de-duplication): 1097

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Urinary Bladder Neoplasms/
2. Ureteral Neoplasms/
3. ((bladder* or urethra* or ureter* or urin* or urotheli* or renal pelvis or calice*) adj3 (cancer* or carcinoma* or adenoma* or adenocarcinoma* or squamous or neoplas* or tumo?r* or malignan*)).tw.
4. exp Carcinoma, Transitional Cell/
5. or/1-4
6. exp Radiotherapy/
7. exp Radiation/
8. exp Radiotherapy Dosage/
9. exp Dose Fractionation/
10. Pelvis/
11. exp Urinary Bladder/
12. or/6-9
13. 10 or 11
14. 12 and 13
15. ((palliat* or pelvi* or bladder) adj3 (radiat* or irradiat* or radiotherap*)).tw.
16. 14 or 15
17. 5 and 16
18. exp Palliative Care/
19. (palliat* adj (care* or medicine or therap*)).tw.
20. "end of life care".tw.
21. or/18-20
22. 5 and 21
23. 17 or 22

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	66	2	03/06/2014
Premedline (Jun 2, 2014)	42	3	03/06/2014
Embase	403	7	03/06/2014
Cochrane Library	17	0	03/06/2014
Psychinfo	0	0	03/06/2014
Web of Science (SCI & SSCI)	549	5	03/06/2014

Total References retrieved (after de-duplication): 10

Topic J4: What is the best way to manage cancer related ureteric obstruction in patients with bladder cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	897	320	04/02/2013
Premedline	Feb 4, 2013	18	10	05/02/2013
Embase	1974 -	1182	359	07/02/2013
Cochrane Library	As per database	13	3	05/02/2013
Web of Science (SCI & SSCI)	1970 -	1935	289	12/02/2013
AMED	1985 -	5	4	05/02/2013
Psycinfo	1806 -	0	0	05/02/2013

Total References retrieved (after de-duplication): 554

Medline search strategy *(This search strategy is adapted to each database)*

1 Ureteral Obstruction/
2 (ureter$ adj3 obstruction).tw.
3 1 or 2
4 exp Stents/
5 stent.tw.
6 Nephrostomy, Percutaneous/
7 nephrostom$.tw.
8 exp Urinary Diversion/
9 (urinary adj3 diver$).tw.
10 or/4-9
11 exp Urinary Bladder Neoplasms/
12 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
13 exp Carcinoma, Transitional Cell/
14 (tcc or transitional cell).mp.
15 exp Ureteral Neoplasms/
16 bladder neoplasms/
17 urethral neoplasms/
18 ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
19 or/11-18
20 3 and 19
21 3 and 10
22 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$).mp.
23 21 and 22
24 20 or 23
25 Urethral Obstruction/ or Urinary Bladder Neck Obstruction/
26 (obstructive adj uropath$).tw.
27 25 or 26
28 10 and 22 and 27
29 24 or 28

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	47	5	02/06/2014
Premedline (May 20, 2014)	31	6	02/06/2014
Embase	197	29	02/06/2014
Cochrane Library	1	0	02/06/2014
Cinahl	6	0 (after search de-dup)	02/06/2014
Psychinfo	0	0	02/06/2014
AMED	0	0	02/06/2014
Web of Science (SCI & SSCI)	251	15	02/06/2014

Total References retrieved (after de-duplication): 36

Topics L1 & L2: What specific interventions are most effective for patients with incurable bladder cancer and intractable bleeding? What specific interventions are most effective for patients with incurable bladder cancer and pelvic pain?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	474	115	19/08/2013
Premedline	Aug 19, 2013	56	1	20/08/2013
Embase	1974 -	1464	172	20/08/2013
Cochrane Library	As per database	114	3	20/08/2013
Web of Science (SCI & SSCI)	1970 -	1246	76	21/08/2013
AMED	1985 -	2	2	20/08/2013
Psycinfo	1806 -	0	0	20/08/2013
Cinahl	1937 -	26	1	20/08/2013

Total References retrieved (after de-duplication): 241

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	642	59	27/08/2013
Premedline	Aug 26, 2013	165	19	27/08/2013
Embase	1974 -	4547	330	04/09/2013
Cochrane Library	As per database	147	14	28/08/2013
Web of Science (SCI & SSCI)	1970 -	2387	61	30/08/2013
AMED	1985 -	9	2	28/08/2013
Psycinfo	1806 -	98	30	28/08/2013
Cinahl	1937 -	70	7	28/08/2013

Total References retrieved (after de-duplication): 429

Medline search strategy *(This search strategy is adapted to each database)*

Topic L1

1. exp urinary bladder neoplasms/
2. (bladder adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3. exp carcinoma, transitional cell/
4. (tcc or transitional cell).mp.
5. exp ureteral neoplasms/
6. bladder neoplasms/
7. urethral neoplasms/
8. ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous or neoplas$ or tumo?r$ or malignan$)).tw.
9. or/1-8
10. (bladder adj3 (haemorrhag$ or hemorrhag$ or bleed$)).tw.
11. (intract$ adj3 (hematuria or haematuria or haemorrhag$ or hemorrhag$ or bleed$ or bladder)).tw.
12. (macrohematuria or macrohaematuria).tw.
13. ((hemorrhagic or haemorrhagic) adj2 cystitis).tw.
14. (massive adj bleed$).tw.
15. ((massive or chronic or gross or terminal or total) adj (hematuria or haematuria)).tw.
16. or/10-15
17. 9 and 16
18. exp Hemorrhage/
19. exp Urinary Bladder/
20. 18 and 19
21. 16 and 20
22. 17 or 21
23. exp Hematuria/
24. (hematuria or haematuria).tw.
25. 23 or 24
26. 16 and 25
27. (haemorrhag$ or hemorrhag$ or bleed$ or hematuria or haematuria).tw.
28. Formaldehyde/
29. (formaldehyde or formalin or formol).tw.
20. exp aluminum compounds/ or alum compounds/
31. alum.tw.
32. Hyperbaric Oxygenation/
33. Hyperbaric oxygen therapy.mp.
34. (HBO or HBOT).tw.
35. exp Embolization, Therapeutic/
36. emboli?ation.mp.
37. Tranexamic Acid/
38. Tranexamic Acid.tw.
39. Lysteda.tw.
40. Hydrostatic Pressure/
41. hydrostatic pressure.tw.
42. Pentosan Sulfuric Polyester/
43. pentosan polysulphate.tw.
44. or/28-43
45. 26 and 44
46. 9 and 27 and 44
47. 45 or 46
48. (palliative adj (radiation or radiotherapy or irradiation or resect$ or TURBT or cystectom$ or chemotherap$ or chemoradiation)).tw.
49. 26 and 48
50. 47 or 49

Topic L2

1-9 (as per lines 1-9 of Topic L1)

10. exp Pain/ or exp Pain, Intractable/
11. pain.mp.
12. 10 or 11
13. 9 and 12
14. (bladder adj pain).tw.
15. (intractable adj pain).tw.
16. (pelvic adj pain).tw.
17. or/14-16
18. (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$).tw.
19. 17 and 18
20. 13 or 19

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on bladder cancer.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	35	1	02/06/2014
Premedline (May 30, 2014)	68	2	02/06/2014
Embase	352	6	02/06/2014
Cochrane Library	6	0	02/06/2014
Cinahl	6	0	02/06/2014
Psychinfo	0	0	02/06/2014
AMED	0	0	02/06/2014
Web of Science (SCI & SSCI)	113	6	02/06/2014

Total References retrieved (after de-duplication): 13

Database name	No of references found	No of references retrieved	Finish date of search
Medline (Pubmed checked)	140	3	03/06/2014
Premedline (Jun 2, 2014)	198	5	03/06/2014
Embase	889	19	03/06/2014
Cochrane Library	37	1	03/06/2014
Cinahl	9	0	03/06/2014
Psychinfo	10	1	03/06/2014
AMED	0	0	03/06/2014
Web of Science (SCI & SSCI)	246	2	03/06/2014

Total References retrieved (after de-duplication): 25

NATIONAL COLLABORATING CENTRE FOR CANCER

Bladder Cancer Clinical Guideline **Health Economics**

1. Literature search details

Database name	No of references found	Finish date of search
Medline (2010 onwards, HE filter)	72	15/05/2012
Premedline (May 9, 2012)	16	11/05/2012
Embase (2010 onwards, HE filter)	272	15/05/2012
Cochrane: HTA	28	15/05/2012
Cochrane: NHSEED	42	15/05/2012
HEED	180	11/07/2013

Total References retrieved (after de-duplication): 361

Medline search strategy *(This search strategy is adapted to each database)*

1. exp urinary bladder neoplasms/
2. (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3. exp carcinoma, transitional cell/
4. (tcc or transitional cell).mp.
5. exp ureteral neoplasms/
6. bladder neoplasms/
7. urethral neoplasms/
8. ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
9. or/1-8

2. Any further comments

A full search of HTA, NHSEED and HEED was undertaken with no date limit to ensure full coverage of topics for the economic plan and for dealing with different health economic analyses. SIGN Health Economics filter applied to the guideline population search for Medline/Premedline and Embase from 2010 onwards.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 15/05/2012 onwards for the first update, and then 18/11/2013 onwards for the second update.

Database name	No of references found	Finish date of search
Medline (2012 onwards, HE filter)	47	18/11/2013
Premedline (Nov 15, 2013)	32	18/11/2013
Embase (2012 onwards, HE filter)	400	18/11/2013
Cochrane: HTA	6	18/11/2013
Cochrane: NHSEED	11	18/11/2013
HEED	7	18/11/2013

Total References retrieved (after de-duplication): 435 + 5 in HEED

Database name	No of references found	Finish date of search
Medline (2013 onwards, HE filter)	60	28/05/2014
Premedline (May 27, 2014)	13	28/05/2014
Embase (2013 onwards, HE filter)	215	28/05/2014
Cochrane: HTA (2013 onwards)	0	28/05/2014
Cochrane: NHSEED (2013 onwards)	5	28/05/2014
HEED	1	28/05/2014

Total References retrieved (after de-duplication): 233 + 1 in HEED

Appendix 3 Excluded health economic papers

Institute-of-Applied-Health-Sciences-. "Systematic review of the clinical and cost-effectiveness, and economic evaluation, of photodynamic diagnosis and novel urine biomarker tests in the detection and follow-up of bladder cancer (Project record)." Aberdeen.: Institute of Applied Health Sciences (2007).

Reason: Summary of analysis in Mowatt HTA (2010)

-The-Netherlands-Organisation-for-Health-Research-and-Development-. "Cost-effectiveness of follow-up of patients with superficial bladder cancer (Project record)." The Netherlands.Organisation.for Health Research and Development. (2001).

Reason: Non-English language study

-VA-Technology-Assessment-Program-. "Bladder cancer surveillance (Structured abstract)." Boston.: VA.Technology Assessment Program. (2007).

Reason: Cost-effectiveness analysis was not considered

Bobman, J. "Evaluating cost and quality of life in non-muscle invasive bladder cancer." Journal of Urology 189.4 Supp 1 (2013): e174.

Reason: Non-comparative cost-utility analysis

Brausi, M. A., et al. "The use of local anesthesia with N-DO Injector (Physion) for transurethral resection (TUR) of bladder tumors and bladder mapping: preliminary results and cost-effectiveness analysis (Provisional abstract)." European Urology 52 (2007): 1407-13.

Reason: Not a full cost-effectiveness analysis

Bredin, H. C. One-stage radical cystectomy for bladder carcinoma: operative mortality, cost/benefit analysis. Journal of Urology 117:447-451. 1977. Ref Type: Abstract

Reason: Cost analysis, not a full cost-effectiveness analysis.

Burger, M. Photodynamic diagnostics and noninvasive bladder cancer: is it cost-effective in long-term application? A Germany-based cost analysis. European Urology 52(1):142-147. 2007. Ref Type: Abstract

Reason: Cost study, not cost-effectiveness analysis

Chamie, K. "Recurrence of high-risk bladder cancer: A population-based analysis." Cancer 119.17 (2013): 3219-22.

Reason: Not cost-utility analysis

Davenport, K., F. X. Keeley, Jr., and A. G. Timoney. "Audit of safety, efficacy, and cost-effectiveness of local anaesthetic cystodiathermy." Annals of the Royal College of Surgeons of England 92.8 (2010): 706-09.

Reason: Not cost-effectiveness analysis

de-Bekker-Grob, E. W., et al. "Non-muscle-invasive bladder cancer surveillance for which cystoscopy is partly replaced by microsatellite analysis of urine: a cost-effective alternative? (Provisional abstract)." BJU International 104.1 (2009): 41-47.

Reason: Not cost-utility analysis

Dinh, T. "Comparative effectiveness of conservative therapy versus cystectomy for non-muscle invasive bladder cancer patients." Value in Health Conference.var.pagings (2013): 7.

Reason: Abstract only

Dinh, T. A. "A novel simulation model of non-muscle invasive bladder cancer: A platform for a virtual randomized trial of conservative therapy vs cystectomy in BCG refractory patients." Journal of Urology Conference.var.pagings (2012): 4-e432.

Reason: Abstract only

Erickson, L. "Assessment of photodynamic therapy using porfimer sodium for esophageal, bladder and lung cancers (Structured abstract)." Montreal: Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (2004): 54.

Reason: Review does not identify any cost-effectiveness analyses on bladder cancer

Faithfull, S., et al. "Evaluation of nurse-led follow up for patients undergoing pelvic radiotherapy (Structured abstract)." British Journal of Cancer 85.12 (2001): 1853-64.

Reason: Not cost-effectiveness analysis

Falebita, O. A., G. Lee, and P. Sweeney. "Urine cytology in the evaluation of urological malignancy revisited: is it still necessary?" Urologia Internationalis 84.1 (2010): 45-49.

Reason: Not full cost-effectiveness analysis

Feifer, A., et al. "Contemporary cost analysis of single instillation of mitomycin after transurethral resection of bladder tumor in a universal health care system." Urology 76.3 (2010): 652-56.

Reason: Not cost-utility analysis

Fradet, Y. "Cost-effectiveness of fluorescent cystoscopy for noninvasive papillary tumors." Journal of Urology 187.5 (2012): 1537-39.

Reason: not full cost-effectiveness

Garfield, S. S., et al. "The cost-effectiveness of blue light cystoscopy in bladder cancer detection: United States projections based on clinical data showing 4.5 years of follow up after a single hexaminolevulinate hydrochloride instillation." Canadian Journal of Urology 20.2 (2013): 6682-89.

Reason: Not a cost-utility analysis that meets NICE requirements

Green, D. A. "Cost-effectiveness (CE) of different management strategies for low-risk non-muscle invasive bladder cancer(NMIBC)." Journal of Urology Conference.var.pagings (2012): 4-e675.

Reason: Abstract only (full paper has also been identified - Green et al. 2013)

Health, Technology Assessment. "Vinflunine for the second line treatment of transitional cell carcinoma of the urothelial tract (Project record)." Health Technology Assessment (2011).

Reason: NICE STA on Vinflunine. Not to be covered in guideline

Holmang, S. "High-grade non-muscle-invasive bladder cancer: Is re-resection necessary in all patients before intravesical bacillus Calmette-Guerin treatment?" Scandinavian Journal of Urology 47.5 (2013): 363-69.

Reason: Not cost-utility analysis

Hunt, M. T. Cost-effectiveness of investigations for invasive bladder cancer. Journal of the Royal Society of Medicine 80(3):143-144. 1987. Ref Type: Abstract

Reason: Effectiveness not measured using LYs or QALYs.

Jensen, J. B. "Narrow-band imaging (NBI) in flexible cystoscopy improves diagnosis of bladder pathology in the outpatient clinic." European Urology, Supplements 11.1 (2012): e446-446a.

Reason: Abstract only.

Kamat, A. M., et al. "Prospective trial to identify optimal bladder cancer surveillance protocol: reducing costs while maximizing sensitivity." BJU International 108.7 (2011): 1119-23.

Reason: Not cost-utility analysis, cost per detection only

Karakiewicz, P. I., M. Sun, and M. Azizi. "Comparative effectiveness of transurethral resection of bladder tumors and office fulguration for recurrent bladder tumors." Journal of Comparative Effectiveness Research 3.2 (2014): 131-33.

Reason: Not cost-utility analysis

Lachaine, J., L. Valiquette, and R. Crott. "Economic evaluation of NMP22 in the management of bladder cancer (Structured abstract)." Canadian Journal of Urology 7.2 (2000): 974-80.

Reason: Not full cost-effectiveness analysis

Lammers, R. J. M. "The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive bladder cancer: A systematic review." European Urology 60.1 (2011): 81-93.

Reason: Does not include cost-effectiveness analysis

Lee, C. T. Economic and humanistic consequences of preventable bladder tumor recurrences in nonmuscle invasive bladder cancer cases. Journal of Urology 188(6):2114-2119. 2012. Ref Type: Abstract

Reason: Not a full cost-utility analysis

London, S. "Analysis favors cystoscopy alone for bladder surveillance." Oncology Report.MARCH-APRIL (2010): 20.

Reason: Opinion article based on Karam et al. 2010

Lotan, Y. "Cost-effectiveness of fluorescent cystoscopy for noninvasive papillary tumors: con." Journal of Urology 187.5 (2012): 1538-39.

Reason: Not cost-utility analysis

Lotan, Y. "Is robotic surgery cost-effective: No." Current Opinion in Urology 22.1 (2012): 66-69.

Reason: Not full cost-effectiveness analysis, assumes equivalence in effectiveness and compares costs.

Lotan, Y. and C. G. Roehrborn. "Cost-effectiveness of a modified care protocol substituting bladder tumor markers for cystoscopy for the followup of patients with transitional cell carcinoma of the bladder: a decision analytical approach (Structured abstract)." Journal of Urology 167.1 (2002): 75-79.

Reason: Discussion article

Malmstrom, P. U., et al. "Fluorescence-guided transurethral resection of bladder cancer using hexaminolevulinate: analysis of health economic impact in Sweden (Provisional abstract)." Scandinavian Journal of Urology and Nephrology 43.3 (2009): 192-98.

Reason: not full cost-effectiveness analysis

Manglik, N. "Evaluation of urovysion FISH and cytology testing - Concordance and cost effectiveness comparison between cotesting vs. non-cotesting samples." Laboratory Investigation Conference.var.pagings (2011): 209A.

Reason: not a comparison relevant to a topic in the guideline

Marchetti, A. Management of patients with bacilli calmette-guerin-refractory carcinoma in situ of the urinary bladder: cost implications of a clinical trial for valrubicin. Clinical Therapeutics 22(4):422-438. 2000. Ref Type: Abstract

Reason: Not cost-utility analysis

Marteau, F. "Cost-effectiveness of the optical imaging agent hexaminolevulinate for patients undergoing initial transurethral resection of non-muscle invasive bladder cancer tumours." European Urology, Supplements Conference.var.pagings (2013): 6.

Reason: Abstract only

Martinez-Pineiro, J. A. The role of neoadjuvant chemotherapy for invasive bladder cancer. British Journal of Urology 82:33-42. 1998. Ref Type: Abstract

Reason: Not cost-utility analysis

Mitra, N. A propensity score approach to estimating the cost-effectiveness of medical therapies from observational data. Health Economics 14(8):805-815. 2005. Ref Type: Abstract

Reason: Not cost-utility analysis

Mundy, L. and J. E. Hiller. "NMP22 BladderChek Diagnostic test for bladder cancer: update (Structured abstract)." Adelaide.: Adelaide.Health Technology Assessment on behalf.of National Horizon.Scanning.Unit. (2009).

Reason: Only includes brief summary of a previous CEA

Neymark, N. Economics of urinary tract cancers: state of the art. European Urology 31(Suppl1):72-81. 1997. Ref Type: Abstract

Reason: Review concludes that there is no high quality CEAs available. Too old to be useful

Novicki, D. E., et al. "Cost-effective evaluation of indeterminate urinary cytology (Structured abstract)." Journal of Urology 160.3 Part 1 (1998): 734-36.

Reason: Not full cost-effectiveness analysis

Onishi, T. "The benefit of continuous saline bladder irrigation after transurethral resection in non-muscular invasive bladder cancer." Journal of Urology Conference.var.pagings (2011):

Reason: Not full cost-effectiveness analysis

Otto, W., et al. "Photodynamic diagnosis for superficial bladder cancer: do all risk-groups profit equally from oncological and economic long-term results?" Clinical Medicine Oncology 3 (2009): 53-58.

Reason: Not full cost-effectiveness analysis

Panou, C. Urinary test use for cancer screening: an underestimated health economics pitfall? Journal of Laboratory and Clinical Medicine 143(6):366-367. 2004. Ref Type: Abstract

Reason: Not full cost-effectiveness analysis

Park, D. S., et al. "An analysis of the efficacy, safety, and cost-effectiveness of fulguration under local anesthesia for small-sized recurrent masses: a comparative analysis to transurethral resection of bladder tumors in a matched cohort." Journal of Endourology 27.10 (2013): 1240-44.

Reason: not cost-utility analysis

Risager, M. "Reduction of recurrence in non-muscle invasive bladder cancer using photodynamic diagnosis and immediate post-TUR-B chemoprophylaxis." Urology Conference.var.pagings (2013): 3-S21.

Reason: Conference abstract only.

Schlake, A., et al. "NMP-22, urinary cytology, and cystoscopy: a 1 year comparison study." Canadian Journal of Urology 19.4 (2012): 6345-50.

Reason: Not cost-utility analysis.

Schwentner, C. "Second-line application of urine-based molecular markers in transitional carcinoma diagnostics - A contribution to cost effectiveness." European Urology, Supplements Conference.var.pagings (2011): 2.

Reason: Abstract only.

See, W. A. Should we screen for bladder cancer in a high-risk population? A cost per life-year saved analysis. Urologic Oncology 25(3):276-277. 2007. mRef Type: Abstract

Reason: Not cost-utility analysis. Screening not considered in guideline.

Shalom, D. "The use of cystoscopy to detect urothelial carcinoma in patients with pelvic organ prolapse and asymptomatic microscopic hematuria." Journal of Pelvic Medicine and Surgery Conference.var.pagings (2010): 2-S28.

Reason: Not full cost-effectiveness analysis.

Smith, A. "Risk-specific intensity of surveillance practices in non-muscle-invasive bladder cancer: Results from the BCAN/SUO/AUA/LUGPA electronic survey." Journal of Clinical Oncology 29.7 Supp 1 (2011).

Reason: Not cost-utility analysis.

Stevenson S., Deibert. "Cost effectiveness analysis of neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer." Journal of Urology 189.4 Supp 1 (2013): e170.

Reason: Abstract only.

Uchida, A., et al. "Intravesical instillation of bacille Calmette-Guerin for superficial bladder cancer: cost-effectiveness analysis (Provisional abstract)." Urology 69.2 (2007): 275-79.

Reason: Not a cost-utility analysis (effectiveness is measured using recurrence free survival)

van Kessel, K. E. FGFR3 mutation analysis in voided urine samples to decrease cystoscopies and cost in nonmuscle invasive bladder cancer surveillance: a comparison of 3 strategies. Journal of Urology 189(5):1676-1681. 2013. Ref Type: Abstract

Reason: Not cost-utility analysis.

Van Rhijn, B. W. G. "Prospective trial to identify optimal bladder cancer surveillance protocol: Reducing costs while maximizing sensitivity." BJU International 108.7 (2011): 1123-24.

Reason: Editorial article not cost-effectiveness analysis

Wang, W. "Intravesical therapy following treatment of non-muscle invasive bladder cancer." International Journal of Urology 19 (2012): 36.

Reason: Abstract only.

Wood, D. P. "Contemporary cost analysis of single instillation of mitomycin after transurethral resection of bladder tumor in a universal health care system." Journal of Urology 185.6 (2011): 2100-01.

Reason: Not cost-effectiveness analysis - cost analysis that assumes similar effectiveness

Zaak, D., et al. "Routine use of photodynamic diagnosis of bladder cancer: practical and economic issues (Provisional abstract)." European Urology, Supplements 7.7 (2008): 536-41.

Reason: not full cost-effectiveness analysis

Zehnder, P. "Cost-effectiveness of open versus laparoscopic versus robotic-assisted laparoscopic cystectomy and urinary diversion." Current Opinion in Urology 21.5 (2011): 415-19.

Reason: Review of economic studies but no cost-effectiveness analyses were identified

Zippe, C., L. Pandrangi, and A. Agarwal. "NMP22 is a sensitive, cost-effective test in patients at risk for bladder cancer (Structured abstract)." Journal of Urology 161.1 (1999): 62-65.

Reason: Not full cost-effectiveness analysis