

Surveillance proposal consultation document

2019 surveillance of bladder cancer: diagnosis and management (NICE guideline NG2)

Surveillance proposal

We propose to not update the guideline on [bladder cancer: diagnosis and management](#).

During surveillance editorial or factual corrections were identified, which will be addressed through editorial amendments.

Reasons for the proposal to not update the guideline

The majority of evidence was found to be consistent with the current guideline recommendations. Improvements were seen in the area of robotic cystectomy for some patient outcomes, however as the guideline does not currently state which method of radical cystectomy should be used, there is unlikely to be an impact at this time. The evidence found for urinary biomarkers supports the current recommendations in this area.

For further details and a summary of all evidence identified in surveillance, see [appendix A](#) below.

Overview of 2019 surveillance methods

NICE's surveillance team checked whether recommendations in [bladder cancer: diagnosis and management](#) (NICE guideline NG2) remain up to date.

The surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- A search for new or updated Cochrane reviews.
- Examining related NICE guidance and quality standards and NIHR signals.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.

- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders (this document).

For further details about the process and the possible update decisions that are available, see [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to specific parts of the guideline. A focused search was undertaken for the areas of robotic assisted radical cystectomy and urinary biomarkers. A search for Cochrane reviews was also undertaken as part of the initial intelligence gathering. These searches were selected following input from topic experts and evidence found in the initial intelligence gathering.

We found 29 studies in a search for systematic reviews, randomised controlled trials and diagnostic accuracy studies published between 01 April 2014 and 20 November 2018.

We also included:

- 1 relevant study from a total of 9 identified by topic experts (this study was also identified through our search)

From all sources, we considered 29 studies to be relevant to the guideline.

See [appendix A: summary of evidence from surveillance](#) below for details of all evidence considered, and references.

Selecting relevant studies

For the search on urinary biomarkers, studies were included for adults aged over 18 with suspected, newly diagnosed or recurrent bladder cancer. Studies were only included if they compared a biomarker to the current recommended method, cystoscopy and if sensitivity and specificity results were stated. For the search on robotic cystectomy, only studies in adults aged over 18 with newly diagnosed or recurrent bladder cancer or newly diagnosed cancer of the urethra were included. Studies were required to have standard open cystectomy as a comparator.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 15 studies were assessed as having the potential to change recommendations; therefore we plan to check the publication status regularly, and evaluate the impact of the results on current

recommendations as quickly as possible. These studies covered robotic cystectomy, intravesical therapy, tumour imaging, quality of life, and chemotherapy.

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to the guideline.

We sent questionnaires to 10 topic experts and received 6 responses.

Topic experts highlighted the new evidence available for immunotherapy such as pembrolizumab, however this area is covered by technology appraisals, TA519 and TA522 and is currently limited to use within the cancer drugs fund. As such we will not be covering immunotherapy in this surveillance review. Time to definitive treatment for muscle-invasive bladder cancer was also raised, as treatment is classed as commenced when the initial transurethral resection of bladder tumour (TURBT) has been performed. As no evidence for time to treatment was found during our initial intelligence gathering, this was not part of our focused search.

Other sources of information

We considered all other correspondence received since the guideline was published. A query was raised at the 2014 consultation regarding photodynamic versus white-light guided treatment of non-muscle-invasive bladder cancer. The study aims to compare time to recurrence for each of the 2 methods and evaluate the cost-effectiveness. An ongoing study in this area was highlighted which will be tracked and assessed for impact once results are available. This study was also highlighted by a topic expert and identified during our search for ongoing studies.

Views of stakeholders

Stakeholders are consulted on all surveillance reviews except if the whole guideline will be updated and replaced. Because this surveillance proposal is to not update the guideline, we are consulting with stakeholders.

See [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual for more details on our consultation processes.

Equalities

No equalities issues were identified during the surveillance process.

Editorial amendments

During surveillance of the guideline we identified the following points in the guideline that should be amended:

- Recommendation 1.1.6 links to [smoking cessation services](#) (PH10) and [brief interventions and referral for smoking cessation](#) which have both been replaced with [NICE guideline NG92](#). This recommendation will be refreshed to state: Offer smoking cessation support to all people with bladder cancer who smoke, in line with NICE guideline NG92: [Stop smoking interventions and services](#).
- Recommendation 1.4.3 has a cross referral to [low-risk](#). This should hyperlink to recommendation 1.3, however this link goes to recommendation 1.2. The low-risk hyperlink will be updated to link to [recommendation 1.3](#).
- We will add a cross referral to the bladder cancer pathway from recommendations 1.7.7 and 1.7.8 to highlight the new technology appraisals that are available.

CSG2: Improving outcomes in urological cancers

- There are inconsistencies between the related guideline [CSG2: Improving outcomes in urological cancers](#) and the NICE guideline on bladder cancer in relation to grading/staging, neo-adjuvant chemotherapy, superficial tumours and terminology used. CSG2 will be amended to remove the inconsistencies.

Overall surveillance proposal

After considering all evidence and other intelligence and the impact on current recommendations, we propose that no update is necessary.

Appendix A: Summary of evidence from surveillance

2018 surveillance of [Bladder cancer: diagnosis and management](#) (2015) NICE guideline NG2

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a view on the need to update each section of the guideline. We searched for new evidence related to 2 areas of the guideline which were highlighted by topic experts as potentially having new evidence that could change recommendations:

- Urinary biomarkers
- Robotic cystectomy

[Information and support for people with bladder cancer](#)

Recommendations in this section of the guideline

- 1.1.1 Follow the recommendations on communication and patient-centred care in NICE's guideline on [patient experience in adult NHS services](#) and the advice in NICE's guidelines on [improving outcomes in urological cancers](#) and [improving supportive and palliative care for adults with cancer](#) throughout the person's care.
- 1.1.2 Offer clinical nurse specialist support to people with bladder cancer and give them the clinical nurse specialist's contact details.
- 1.1.3 Ensure that the clinical nurse specialist:
 - acts as the key worker to address the person's information and care needs
 - has experience and training in bladder cancer care.
- 1.1.4 Use a holistic needs assessment to identify an individualised package of information and support for people with bladder cancer and, if they wish, their partners, families or carers, at key points in their care such as:
 - when they are first diagnosed
 - after they have had their first treatment
 - if their bladder cancer recurs or progresses
 - if their treatment is changed

- if palliative or end of life care is being discussed.

1.1.5 When carrying out a holistic needs assessment, recognise that many of the symptoms, investigations and treatments for bladder cancer affect the urogenital organs and may be distressing and intrusive. Discuss with the person:

- the type, stage and grade of their cancer and likely prognosis
- treatment and follow-up options
- the potential complications of intrusive procedures, including urinary retention, urinary infection, pain, bleeding or need for a catheter
- the impact of treatment on their sexual health and body image, including how to find support and information relevant to their gender
- diet and lifestyle, including physical activity
- smoking cessation for people who smoke
- how to find information about bladder cancer, for example through information prescriptions, sources of written information, websites or DVDs
- how to find support groups and survivorship programmes
- how to find information about returning to work after treatment for cancer
- how to find information about financial support (such as free prescriptions and industrial compensation schemes).

1.1.6 Offer smoking cessation support to all people with bladder cancer who smoke, in line with NICE's guidelines on [smoking cessation services](#) and [brief interventions and referral for smoking cessation](#).

1.1.7 Offer people with bladder cancer and, if they wish, their partners, families or carers, opportunities to have discussions at any stage during their treatment and care with:

- a range of specialist healthcare professionals, including those who can provide psychological support
- other people with bladder cancer who have had similar treatments.

1.1.8 Clinicians caring for people with bladder cancer should ensure that there is close liaison between secondary and primary care with respect to ongoing and community-based support.

1.1.9 Trusts should consider conducting annual bladder cancer patient satisfaction surveys developed by their urology multidisciplinary team and people with bladder cancer, and use the results to guide a programme of quality improvement.

Surveillance proposal

No new information was identified at any surveillance review.

This section of the guideline should not be updated.

Editorial amendments

Recommendation 1.1.6 links to [smoking cessation services](#) (PH10) and [brief interventions and referral for smoking cessation](#) which have both been replaced with [NICE guideline NG92](#). This recommendation will be amended to state: Offer smoking cessation support to all people with bladder cancer who smoke, in line with NICE guideline NG92: [Stop smoking interventions and services](#).

Diagnosing and staging bladder cancer

Recommendations in this section of the guideline

Diagnosis

- 1.2.1 Do not substitute urinary biomarkers for cystoscopy to investigate suspected bladder cancer or for follow-up after treatment for bladder cancer, except in the context of a clinical research study.
- 1.2.2 Consider CT or MRI staging before transurethral resection of bladder tumour (TURBT) if muscle-invasive bladder cancer is suspected at cystoscopy.
- 1.2.3 Offer white-light-guided TURBT with one of photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker test (such as UroVysion using fluorescence in-situ hybridisation [fluorescence in situ hybridisation (FISH)], ImmunoCyt or a nuclear matrix protein 22 [NMP22] test) to people with suspected bladder cancer. This should be carried out or supervised by an urologist experienced in TURBT.
- 1.2.4 Obtain detrusor muscle during TURBT.
- 1.2.5 Do not take random biopsies of normal-looking urothelium during TURBT unless there is a specific clinical indication (for example, investigation of positive cytology not otherwise explained).
- 1.2.6 Record the size and number of tumours during TURBT.
- 1.2.7 Offer people with suspected bladder cancer a single-dose of intravesical mitomycin C given at the same time as the first TURBT.

Staging

- 1.2.8 Consider further TURBT within 6 weeks if the first specimen does not include detrusor muscle.

- 1.2.9 Offer CT or MRI staging to people diagnosed with muscle-invasive bladder cancer or [high-risk](#) non-muscle-invasive bladder cancer that is being assessed for radical treatment.
- 1.2.10 Consider CT urography, carried out with other planned CT imaging if possible, to detect upper tract involvement in people with new or recurrent high-risk non-muscle-invasive or muscle-invasive bladder cancer.
- 1.2.11 Consider CT of the thorax, carried out with other planned CT imaging if possible, to detect thoracic malignancy in people with muscle-invasive bladder cancer.
- 1.2.12 Consider fluorodeoxyglucose positron emission tomography (FDG PET)-CT for people with muscle-invasive bladder cancer or high-risk non-muscle-invasive bladder cancer before radical treatment if there are indeterminate findings on CT or MRI, or a high risk of metastatic disease (for example, T3b disease).

Surveillance proposal

This section of the guideline should not be updated.

Diagnosing and staging

2018 surveillance summary

Urinary biomarkers

Bladder cancer diagnosis

A meta-analysis(1) of 24 studies (n=8848 patients) assessed nuclear matrix protein 22 (NMP-22) for diagnosis of bladder cancer compared to cystoscopy. Sensitivity for NMP-22 was 0.71 and specificity was 0.80, AUC was 0.7846. The results do not indicate that NMP-22 should replace cystoscopy.

A prospective blinded study(2) assessed a urine test for 8 DNA mutations and methylation biomarkers compared to flexible cystoscopy in patients with gross haematuria. Urine samples were collected before (n=461) and after (n=444) cystoscopy. The urine biomarker test had a sensitivity and specificity of 97% and 76.9% respectively. Three patients who

had positive urine results but negative cystoscopy findings had a tumour detected at repeat cystoscopy within 16 months.

A prospective blinded validation study(3) (n=525) investigated gene expression in urine samples for bladder cancer diagnosis compared to cystoscopy. Four gene signatures were investigated, with a combination of 2 genes (GS_D2) giving the highest sensitivity (81.48%) and specificity (91.26%). The diagnostic accuracy of the 2 gene signature was statistically associated with tumour size. Accuracy increased with increasing tumour risk but not number of tumours.

Bladder cancer initial detection and recurrence

A systematic review and meta-analysis(4) of 57 studies (number of participants not stated) assessed the accuracy of urinary biomarkers for the detection of new or

recurrent cases of bladder cancer. Wide ranges of sensitivities and specificities were reported amongst different biomarkers, however the results stated that a substantial number of cases of bladder cancer were missed by urinary biomarkers, with poor accuracy for low-stage and grade tumours.

A study(5) investigated the levels of semaphorin 3A (Sema3A) in the urine of patients (n=183) for the detection of bladder cancer compared to cystoscopy results. From 116 patients with positive cystoscopy findings, higher Sema3A levels significantly correlated with urothelial cancer. This was also seen with the number of tumours and levels of Sema3A.

A study(6) (n=147 initial diagnoses, 399 recurrence monitoring) examined the oligonucleotide fluorescence in situ hybridisation (OligoFISH) chromosome probe panel compared to cytology, cystoscopy and pathology for initial bladder cancer diagnosis and recurrence detection. This table displays the results obtained:

	initial diagnosis	recurrence monitoring
accuracy	90.50%	85.20%
sensitivity	96.80%	82.00%
specificity	79.20%	88.40%
PPV	89.20%	87.70%
NPV	93.30%	83.00%

Bladder cancer surveillance

A study(7) investigated 4 urine markers for surveillance of recurrent tumours in patients (n=483) with non-muscle-invasive bladder cancer (NMIBC). Cystoscopy was performed following urinary cytology, UroVysion, FISH, immunocytology and NMP22 ELISA. The abstract does not state

the sensitivities of the single tests however states that they ranged from 66.4 to 74.3%. Results for the urinary biomarker NMP22 in combination with other methods are not stated however the abstract mentions that it “showed remarkable detection rates”.

A prospective single centre study(8) evaluated the detection of bladder cancer recurrence using 2 point of care tests, nuclear matrix protein 22 (NMP22) and UBC Rapid. Patients were grouped as active bladder cancer (n=31) or without disease (n=44) by cystoscopy. All patients had voided urine, bladder washing cytology, NMP22 and UBC Rapid tests completed. Sensitivity for NMP22 was low at 12.9% with 100% specificity. UBC Rapid had sensitivity of 61.3% and specificity of 64.5% however this increased to 77.4% sensitivity when combined with cytology as a dual test.

A study(9) examined the ability to diagnose recurrence of bladder cancer using changes in DNA methylation detected in urine samples compared to surveillance with cytology and cystoscopy. Six biomarkers were used to analyse 368 samples from 90 patients with non-invasive bladder cancer. High sensitivity (86%) and specificity (89%) was seen with a panel of 3 markers, predicting recurrence in 80% of patients.

Primary haematuria

A systematic review and meta-analysis(10) of 17 studies (no. of participants not stated) assessed the diagnostic performance of 6 urinary biomarker tests (AssureMDx, Bladder tumour antigen, CxBladder, NMP22, UroVysion, uCyt+) compared to both FDA approved urinary

biomarkers and cystoscopy for bladder cancer in patients presenting with haematuria. The individual test results were not reported in the abstracts, however sensitivity ranged from 0.67 to 0.95 and specificity from 0.68 to 0.93. The authors state that the results for the AssureMDx suggest it may be useful for triage prior to cystoscopy.

Intelligence gathering

Several ongoing studies have been identified through the surveillance review which are relevant to this section of the guideline:

- An ongoing diagnostic accuracy study was identified which is investigating the use of the [Xpert bladder cancer monitoring test](#) compared to cystoscopy for bladder cancer surveillance.
- An ongoing study was found regarding [en-bloc resection](#) for bladder cancer to prevent shedding of the bladder tumour cells. Transurethral en-bloc resection of bladder tumour is compared to the current method of TURBT to determine if less recurrence is seen in the en-bloc group.
- An ongoing trial is investigating a [new tracer](#) for PET-CT scans for diagnostic imaging of urological tumours.
- Ongoing trials have also been found for [magnetic resonance imaging](#) in patients with muscle-invasive bladder cancer, imaging with [photodynamic guided treatment](#) and [image enhancement systems](#).

These studies will be monitored and results considered for impact on the guideline once available.

Impact statement

Bladder cancer diagnosis

One meta-analysis found that NMP-22 was not as sensitive as cystoscopy for the diagnosis of bladder cancer. Two studies found that testing urine for DNA mutations or gene expression had good results for either sensitivity or specificity but not both. A topic expert highlighted that these sensitivity results were not high enough for clinical use. Neither test was as sensitive as cystoscopy for the detection of bladder cancer.

Bladder cancer initial detection and recurrence

A systematic review found that urinary biomarkers lacked accuracy for the detection of new and recurrent low grade tumours and a number of cases would not be detected. One study found urinary detection of semaphorin 3A to correlate with new or recurrent urothelial cancer. One study found OligoFISH had a reasonably high sensitivity and specificity for initial detection, with slightly lower sensitivity for recurrence detection compared to cystoscopy. However a topic expert commented that the sensitivities reported in the studies were not high enough for clinical use.

Bladder cancer surveillance

One study found 4 urinary biomarkers for bladder cancer surveillance did not have a high sensitivity when compared to cystoscopy. One study found the UBC Rapid point of care test to be superior to

NMP-22 for sensitivity but not specificity, however sensitivity for both tests was low compared to cystoscopy for bladder cancer surveillance. One study found that a panel of 3 biomarkers had good sensitivity and specificity for detecting bladder cancer recurrence using changes in DNA methylation in urine samples compared to standard surveillance with cytology and cystoscopy.

Primary haematuria

A systematic review found that the AssureMDX biomarker test may be a useful tool to triage patients prior to cystoscopy.

The recommendations in NICE guideline NG2 currently state that urinary

biomarkers should not be used in place of cystoscopy for the suspected cancer diagnosis or for follow up after treatment for bladder cancer, however urinary biomarkers may be offered in conjunction with white-light guided TURBT to people with suspected bladder cancer.

Overall, the evidence found at this review supports the current recommendations as limited data is available for each biomarker and sensitivity remains inferior across all markers when compared to cystoscopy. An ongoing trial is being monitored for urinary biomarkers and results will be considered for impact on the guideline when available.

New evidence is unlikely to change guideline recommendations.

Treating non-muscle invasive bladder cancer

Risk classification in non-muscle-invasive bladder cancer

There is no widely accepted classification of risk in non-muscle-invasive bladder cancer. To make clear recommendations for management, the Guideline Development Group developed the consensus classification in the table below, based on the evidence reviewed and clinical opinion.

Risk categories in non-muscle-invasive bladder cancer

Low-risk	Urothelial cancer with any of: <ul style="list-style-type: none"> • solitary pTaG1 with a diameter of less than 3 cm • solitary pTaG2 (low grade) with a diameter of less than 3 cm • any papillary urothelial neoplasm of low malignant potential
Intermediate risk	Urothelial cancer that is not low-risk or high risk, including: <ul style="list-style-type: none"> • solitary pTaG1 with a diameter of more than 3 cm

	<ul style="list-style-type: none"> • multifocal pTaG1 • solitary pTaG2 (low grade) with a diameter of more than 3 cm • multifocal pTaG2 (low grade) • pTaG2 (high grade) • any pTaG2 (grade not further specified) • any low-risk non-muscle-invasive bladder cancer recurring within 12 months of last tumour occurrence
High risk	<p>Urothelial cancer with any of:</p> <ul style="list-style-type: none"> • pTaG3 • pT1G2 • pT1G3 • pTis (Cis) • aggressive variants of urothelial carcinoma, for example micropapillary or nested variants

Recommendations in this section of the guideline

Prognostic markers and risk classification

1.3.1 Ensure that for people with non-muscle-invasive bladder cancer all of the following are recorded and used to guide discussions, both within multidisciplinary team meetings and with the person, about prognosis and treatment options:

- recurrence history
- size and number of cancers
- histological type, grade, stage and presence (or absence) of flat urothelium, detrusor muscle (muscularis propria), and carcinoma in situ
- the risk category of the person's cancer
- predicted risk of recurrence and progression, estimated using a risk prediction tool.

Low-risk non-muscle-invasive bladder cancer

- 1.3.2 For the treatment of low-risk non-muscle-invasive bladder cancer, see [recommendations 1.2.3–1.2.8](#).

Intermediate risk non-muscle-invasive bladder cancer

- 1.3.3 Offer people with newly diagnosed intermediate-risk non-muscle-invasive bladder cancer a course of at least 6 doses of intravesical mitomycin C.
- 1.3.4 If intermediate-risk non-muscle-invasive bladder cancer recurs after a course of intravesical mitomycin C, refer the person's care to a specialist urology multidisciplinary team.

High risk non-muscle-invasive bladder cancer

- 1.3.5 If the first TURBT shows high-risk non-muscle-invasive bladder cancer, offer another TURBT as soon as possible and no later than 6 weeks after the first resection.
- 1.3.6 Offer the choice of intravesical BCG (Bacille Calmette-Guérin) or radical cystectomy to people with high-risk non-muscle-invasive bladder cancer, and base the choice on a full discussion with the person, the clinical nurse specialist and a urologist who performs both intravesical BCG and radical cystectomy. Include in your discussion:
- the type, stage and grade of the cancer, the presence of carcinoma in situ, the presence of variant pathology, prostatic urethral or bladder neck status and the number of tumours
 - risk of progression to muscle invasion, metastases and death
 - risk of understaging
 - benefits of both treatments, including survival rates and the likelihood of further treatment
 - risks of both treatments
 - factors that affect outcomes (for example, comorbidities and life expectancy)
 - impact on quality of life, body image, and sexual and urinary function.

Intravesical BCG

- 1.3.7 Offer induction and maintenance intravesical BCG to people having treatment with intravesical BCG.
- 1.3.8 If induction BCG fails (because it is not tolerated, or bladder cancer persists or recurs after treatment with BCG), refer the person's care to a specialist urology multidisciplinary team.

- 1.3.9 For people in whom induction BCG has failed, the specialist urology multidisciplinary team should assess the suitability of radical cystectomy, or further intravesical therapy if radical cystectomy is unsuitable or declined by the person, or if the bladder cancer that recurs is intermediate- or low-risk.

Radical cystectomy

- 1.3.10 See [recommendations 1.5.4–1.5.7](#) for people who have chosen radical cystectomy.

Recurrent non-muscle-invasive bladder cancer

- 1.3.11 Consider fulguration without biopsy for people with recurrent non-muscle-invasive bladder cancer if they have all of the following:
- no previous bladder cancer that was intermediate- or high-risk
 - a disease-free interval of at least 6 months
 - solitary papillary recurrence
 - a tumour diameter of 3 mm or less.

Managing side effects of treatment

- 1.3.12 Do not offer primary prophylaxis to prevent BCG-related bladder toxicity except as part of a clinical trial.
- 1.3.13 Seek advice from a specialist urology multidisciplinary team if symptoms of bladder toxicity after BCG cannot be controlled with antispasmodics or non-opiate analgesia and other causes have been excluded by cystoscopy.

Surveillance proposal

This section of the guideline should not be updated.

Treating non-muscle-invasive bladder cancer

2018 surveillance summary

A Cochrane review(11) of 3 trials (n=672 participants) assessed intravesical electromotive drug administration for non-muscle-invasive bladder cancer (Ta, T1 or carcinoma in situ (CIS)) using 5 protocols

for pre and postoperative mitomycin C administration. There was uncertainty regarding adverse events for all protocols. Some improvements in time to disease recurrence and time to disease progression were seen for each of the 5 protocols. See table below for full details.

situation		study/population	disease recurrence	disease progression	adverse events
1	Postoperative MMC – EMDA induction versus postoperative Bacillus Calmette – Guérin (BCG) induction.	1 study 72 participants with CIS and concurrent pT1 urothelial carcinoma.	Uncertain on time to recurrence.	No disease progression in either treatment arm at 3 months follow up.	Uncertain.
2	Postoperative MMC-EMDA induction versus MMC-passive diffusion (PD) induction.	1 study 72 participants with CIS and concurrent pT1 urothelial carcinoma.	Postoperative MMC-EMDA induction may reduce disease recurrence RR 0.65, CI 0.44 to 0.98.	No disease progression in either treatment arm at 3 months follow up.	Uncertain.
3	Postoperative MMC-EMDA with sequential BCG induction and maintenance versus postoperative BCG induction and maintenance.	1 study 212 participants with pT1 urothelial carcinoma of the bladder with or without CIS.	Postoperative MMC-EMDA with sequential BCG may result in longer time to recurrence.	May result in longer time to progression.	Uncertain.
4	Single-dose, preoperative MMC-EMDA versus single-dose, postoperative MMC-PD.	1 study 236 participants with primary pTa and pT1 urothelial carcinoma.	Preoperative MMC-EMDA likely results in a longer time to recurrence.	Uncertain about the effect on time to progression.	Uncertain.
5	Single-dose, preoperative MMC-EMDA versus TURBT alone.	1 study 236 participants with primary pTa and pT1 urothelial carcinoma.	Preoperative MMC-EMDA likely results in a longer time to recurrence.	Uncertain about the effect on time to progression.	Uncertain.

A Cochrane review(12) of 5 RCTs (n= 1231 participants) assessed the effect on NMIBC (confirmed Ta or T1) with intravesically administered BCG plus interferon-alpha (IFN- α) compared to intravesical BCG alone. Four studies compared BCG + IFN- α with BCG alone

and 1 compared intravesical BCG with alternating doses of IFN- α to intravesical BCG alone. No clear difference for any outcome was seen except for time to recurrence in the alternating IFN- α group which was significantly shorter. Please see the table below for full results.

BCG +IFN-α versus BCG alone		
primary/secondary outcomes	results	interpretation
time to recurrence	RR 0.76, 95% CI 0.44 - 1.32	no clear difference
time to progression	RR 0.26, 95% CI 0.04 - 1.87	no clear difference
discontinuation due to adverse events	not reported	n/a
disease-specific mortality	RR 0.38, 95% CI 0.05 - 3.05	no clear difference
time to death	not reported	n/a
systemic/local adverse events	not reported	n/a
BCG alternating with INF-α versus BCG alone		
time to recurrence	HR 2.86, 95% CI 1.98 - 4.13	shorter time to recurrence
time to progression	HR 2.39, 95% CI 0.92 - 6.21	no clear difference
discontinuation due to adverse events	RR 2.97, 95% CI 0.31 - 28.09	no clear difference
disease-specific mortality	HR 2.74, 95% CI 0.73 - 10.28	no clear difference
time to death	HR 1.00, 95% CI 0.68 - 1.47	no clear difference
systemic/local adverse events	RR 1.65, 95% CI 0.41 - 6.73	no clear difference

Intelligence gathering

One topic expert highlighted the increasing use of heated intravesical mitomycin C in clinical practice.

An ongoing trial regarding [maintenance therapy](#) for bladder cancer following chemotherapy was also identified. We will monitor the progress of this trial and consider the results when available.

Impact statement

One Cochrane review found that different protocols of mitomycin C may reduce time to disease recurrence and time to disease progression, however there was uncertainty about adverse events for all protocols.

A topic expert suggested that heated mitomycin C is increasingly being used in

clinical practice. The current recommendations do not suggest using heated mitomycin C. NICE has an intervention guideline on this topic - [IPG628](#), which states that intravesical microwave hyperthermia is not recommended due to well recognised adverse events.

One Cochrane review found that intravesical BCG with alternating IFN- α was more effective than BCG alone for time to disease recurrence, with no clear difference in adverse events. However IFN- α is not currently licensed for use in bladder cancer. The recommendations in NG2 currently state to offer intravesical mitomycin C for NMIBC and offer intravesical BCG for high risk cases.

The evidence found for mitomycin C and BCG does not currently suggest that the

recommendations in NG2 should be updated at this time. As IFN- α had limited data on adverse events and is not currently licensed in the UK for bladder cancer treatment, this evidence is unlikely

to affect the recommendations at this time.

New evidence is unlikely to change guideline recommendations.

Follow-up after treatment for non-muscle-invasive bladder cancer

Recommendations in this section of the guideline

- 1.4.1 Refer people urgently to urological services if they have haematuria or other urinary symptoms and a history of non-muscle-invasive bladder cancer.
- 1.4.2 See [recommendation 1.2.1](#) on the use of urinary biomarkers for follow-up after treatment for bladder cancer.

Low-risk non-muscle-invasive bladder cancer

- 1.4.3 Offer people with [low-risk](#) non-muscle-invasive bladder cancer cystoscopic follow-up 3 months and 12 months after diagnosis.
- 1.4.4 Do not use urinary biomarkers or cytology in addition to cystoscopy for follow-up after treatment for low-risk bladder cancer.
- 1.4.5 Discharge to primary care people who have had low-risk non-muscle-invasive bladder cancer and who have no recurrence of the bladder cancer within 12 months.
- 1.4.6 Do not offer routine urinary cytology or prolonged cystoscopic follow-up after 12 months for people with low-risk non-muscle-invasive bladder cancer.

Intermediate risk non-muscle-invasive bladder cancer

- 1.4.7 Offer people with [intermediate-risk](#) non-muscle-invasive bladder cancer cystoscopic follow-up at 3, 9 and 18 months, and once a year thereafter.
- 1.4.8 Consider discharging people who have had intermediate-risk non-muscle-invasive bladder cancer to primary care after 5 years of disease-free follow-up.

High risk non-muscle-invasive bladder cancer

- 1.4.9 Offer people with [high-risk](#) non-muscle-invasive bladder cancer cystoscopic follow-up:
 - every 3 months for the first 2 years **then**
 - every 6 months for the next 2 years **then**

- once a year thereafter.

1.4.10 For people who have had radical cystectomy for high-risk non-muscle-invasive bladder cancer, see [recommendations 1.6.1 and 1.6.2](#).

Surveillance proposal

No new information was identified at any surveillance review.

This section of the guideline should not be updated

Editorial amendments

Recommendation 1.4.3 has a cross referral to [low-risk](#). This should hyperlink to recommendation 1.3, however this link goes to recommendation 1.2. The low-risk hyperlink will be updated to link to [recommendation 1.3](#).

Treating muscle-invasive bladder cancer

Recommendations in this section of the guideline

1.5.1 Ensure that a specialist urology multidisciplinary team reviews all cases of muscle-invasive bladder cancer, including adenocarcinoma, squamous cell carcinoma and neuroendocrine carcinoma, and that the review includes histopathology, imaging and discussion of treatment options.

Neoadjuvant chemotherapy for newly diagnosed muscle-invasive urothelial bladder cancer

1.5.2 Offer neoadjuvant chemotherapy using a cisplatin combination regimen before radical cystectomy or radical radiotherapy to people with newly diagnosed muscle-invasive urothelial bladder cancer for whom cisplatin-based chemotherapy is suitable. Ensure that they have an opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer.

Radical therapy for muscle-invasive urothelial bladder cancer

1.5.3 Offer a choice of radical cystectomy or radiotherapy with a radiosensitiser to people with muscle-invasive urothelial bladder cancer for whom radical therapy is suitable. Ensure that the choice is based on a full discussion between the person and a urologist who performs radical cystectomy, a clinical oncologist and a clinical nurse specialist. Include in the discussion:

- the prognosis with or without treatment
- the limited evidence about whether surgery or radiotherapy with a radiosensitiser is the most effective cancer treatment

- the benefits and risks of surgery and radiotherapy with a radiosensitiser, including the impact on sexual and bowel function and the risk of death as a result of the treatment.

Radical cystectomy

- 1.5.4 Offer people who have chosen radical cystectomy a urinary stoma, or a continent urinary diversion (bladder substitution or a catheterisable reservoir) if there are no strong contraindications to continent urinary diversion such as cognitive impairment, impaired renal function or significant bowel disease.
- 1.5.5 Members of the specialist urology multidisciplinary team (including the bladder cancer specialist urological surgeon, stoma care nurse and clinical nurse specialist) should discuss with the person whether to have a urinary stoma or continent urinary diversion, and provide opportunities for the person to talk with people who have had these procedures.
- 1.5.6 Offer people with bladder cancer and, if they wish, their partners, families or carers, opportunities to have discussions with a stoma care nurse before and after radical cystectomy as needed.

Adjuvant chemotherapy after radical cystectomy for muscle-invasive or lymph-node-positive urothelial bladder cancer

- 1.5.7 Consider adjuvant cisplatin combination chemotherapy after radical cystectomy for people with a diagnosis of muscle-invasive or lymph-node-positive urothelial bladder cancer for whom neoadjuvant chemotherapy was not suitable (because muscle invasion was not shown on biopsies before cystectomy). Ensure that the person has an opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer.

Radical radiotherapy

- 1.5.8 Use a radiosensitiser (such as mitomycin in combination with fluorouracil [5-FU]* or carbogen in combination with nicotinamide**) when giving radical radiotherapy (for example, 64 Gy in 32 fractions over 6.5 weeks or 55 Gy in 20 fractions over 4 weeks) for muscle-invasive urothelial bladder cancer.

Managing side effects of treatment

- 1.5.9 Seek advice from a specialist urology multidisciplinary team if symptoms of bladder toxicity after radiotherapy cannot be controlled with antispasmodics or non-opiate analgesia and other causes have been excluded by cystoscopy.

* At the time of publication (February 2015), mitomycin in combination with fluorouracil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

**Although this use is common in UK clinical practice, at the time of publication (February 2015), carbogen in combination with nicotinamide did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

Surveillance proposal

This section of the guideline should not be updated

Treating muscle-invasive bladder cancer

2018 surveillance summary

Robotic cystectomy

A systematic review and meta-analysis(13) of 24 studies (n=2104 cases) compared robot-assisted radical cystectomy (RARC), laparoscopic radical cystectomy (LRC) and open radical cystectomy (ORC) for treating muscle-invasive bladder cancer. A shorter length of stay, reduced estimated blood loss, lower operating time and lower complication rates were seen with RARC compared to ORC. LRC similarly showed better surgical outcomes compared to ORC. No significant difference in length of stay or estimated blood loss was seen when RARC and LRC were compared, however RARC had a longer operative time.

A systematic review and meta-analysis(14) of 7 studies (n=748 patients) compared RARC and ORC for the primary outcomes of complications and mortality rates. Patient demographics, operating time, estimated blood loss (EBL), transfusion rates and type of urinary diversion were also considered as secondary outcomes. Mortality rates and higher grade

complications were significantly higher in the ORC group, however there was no significant difference between groups for lower grade complications or overall complications. Operating times were significantly higher, however EBL and transfusion rates were significantly lower in the RARC group.

A systematic review and meta-analysis(15) of 4 studies (n=239 patients) examined complication rates for RARC and ORC. Length of stay, time back to work and health-related quality of life (HRQoL) were also considered as secondary outcomes. No significant difference was seen between groups for any outcome, however types of complication (not stated in abstract) differed between the groups.

A systematic review(16) of 105 studies (patient numbers not stated) compared complication rates and perioperative outcomes for RARC compared to ORC and/or LRC. RARC had a longer operating time compared to ORC, and had significantly less blood loss and less time in hospital post-operatively. High grade complication rates and mortality rates were similar between ORC and RARC, however RARC had significantly better overall complication rates and grade 3 complication rates.

A systematic review and meta-analysis(17) of 4 studies (n=239 cases) explored whether RARC could reduce morbidity in the perioperative period for patients undergoing radical cystectomy compared to ORC. No significant differences were seen between groups for length of stay, positive surgical margins, lymph node positives, or grade 2-5 and 3-5 complications. RARC had a significantly longer operating time, lower blood loss and improved time to first food intake compared to ORC.

A systematic review and meta-analysis(18) of 4 RCTs (n=239 patients) examined efficacy of RARC and perioperative morbidity compared to ORC. All patients had extracorporeal urinary diversion. Significantly lower EBL and wound complications were seen with RARC, however a significantly longer operative time was noted compared to ORC. For the outcomes of perioperative morbidity, length of stay, lymph node yield and positive status and positive surgical margins no significant difference was seen between groups. A heterogeneity assessment found differences in operating time indicating that surgical experience may have an influence on the results.

A systematic review and meta-analysis (19) (number of studies not stated) evaluated the safety and efficacy of RARC for the treatment of bladder cancer compared to ORC. Significantly decreased operative time was seen in the ORC group, however the RARC group had significant improvements in the following outcomes: complications, blood loss, time to first food intake, transfusion needs, lymph node yield and positive lymph nodes. No

significant differences were seen between groups for positive surgical margins.

A systematic review and meta-analysis(20) of 19 studies (n= 1779 patients) compared outcomes in RARC and ORC. No difference was seen between groups for positive surgical margins. RARC had significantly longer operative time and significantly lower complication rates, EBL, lower transfusion needs and more lymph node yields compared to ORC.

A meta-analysis(21) (Tang 2018) of 4 RCTs (n=239 patients) compared RARC and ORC for the outcomes of safety and efficacy for radical cystectomy due to bladder cancer. Overall complication rates, length of stay, surgical margins and lymph node yield showed no significant difference between RARC and ORC. RARC had a significantly lower EBL and a longer operative time.

An RCT(22) (n=118 bladder cancer patients scheduled for radical cystectomy) compared RARC and ORC for complications in the perioperative period. The primary outcome was complications as defined by a modified Clavien system up to 90 days post-surgery. Operative time, EBL, pathology outcomes, operative and inpatient costs, comparison of high grade complications and 3 and 6 month quality of life (patient reported) were secondary outcomes. The trial was closed early as the results for complications met futility criteria. Grade 2-5 complication rate was 62% in RARC and 66% in ORC, with significantly lower blood loss but longer operating times in the RARC group. All other secondary outcomes were similar between groups (significance not stated in abstract).

An RCT(23) (n=118) aimed to examine differences in cancer recurrence in patients who had undergone RARC or ORC for the treatment of bladder cancer. This study is a 4 year follow up of the above trial. Outcomes were cancer recurrence, patterns of recurrence and survival outcomes however the authors state that the trial was not sufficiently powered to answer these questions. No difference was seen between groups for any of the 3 listed outcomes. The increase in metastatic sites was increased in ORC however this was not statistically significant. A significantly greater number of local/abdominal sites was observed in the RARC group compared to ORC.

An early phase RCT(24) (n=60) compared ORC, LRC and RARC for the primary outcomes of complication rates at 30 and 90 days post-surgery. Perioperative clinical outcomes and quality of life were secondary outcomes. No significant difference in complication rates was seen post-operatively at 90 days, however rates varied significantly at the 30 day point. No significant differences in quality of life was seen between techniques, however RARC had a significantly longer operating time and ORC has a significantly slower return to oral solids.

An RCT(25) (n=40) compared RARC (n=20) and ORC (n=20) for the outcome of HRQoL using a validated Functional Assessment of Cancer Therapy-Vanderbilt Cystectomy Index questionnaire. HRQoL was assessed peri-operatively and at 3, 6, 9 and 12 months post-surgery. No significant difference was found for either group at any time point. Both groups had returned to baseline levels by 3 months post-surgery. A higher physical wellbeing

score was noted for the RARC group at 6 months post-surgery.

An RCT(26) (n=302) investigated non-inferiority of RARC (n=150) compared to ORC (n=152), with 2 year progression free survival as the primary outcome. Rates of adverse events and 2 year progression free survival were similar between groups, with analysis stating that RARC is non-inferior to ORC.

A cost-effectiveness study(27) compared RARC to ORC for the treatment of bladder cancer. HRQoL and medical costs were compared using a decision analytic model for 100 RARC cases and 96 ORC cases. Fewer transfusions were seen in the RARC group, as were fewer complications compared to the ORC group. No difference between groups was identified for other outcomes such as length of hospital stay, patient demographics or staging. Whilst this study was not based on the UK healthcare system, it found RARC to be more cost effective providing that it could remain able to prevent over 70% of transfusions compared to ORC, despite the higher cost of the RARC surgery.

Hyperbaric oxygenation therapy

A Cochrane review(28) of 19 trials (n=2286 participants) considered the use of hyperbaric oxygenation therapy used with radiotherapy to improve tumour sensitisation. No improvements were seen for bladder cancer and adverse events were reported.

Intelligence gathering

A topic expert highlighted the following areas where ongoing studies are available:

- use of adaptive radiotherapy (using imaging to reduce the amount of healthy tissue targeted by radiotherapy)
- Updated information on adjuvant chemotherapy.

An ongoing trial was found regarding administration of [JX-594](#) intravenously prior to surgery for urological cancers. It is not possible to know how applicable this study will be to bladder cancer until the results are available.

An ongoing trial comparing [RARC to ORC](#) was also identified along with an ongoing trial assessing [HRQoL](#) following radical cystectomy. All ongoing studies will be monitored and results considered for impact on the guideline when available.

Impact statement

Robotic cystectomy

Eight systematic reviews compared RARC to ORC finding that operative time was longer with RARC (5 studies), however improvements were seen with EBL (5 studies), fewer complications (4 studies), lower blood transfusion requirements (2 studies), and a quicker time to diet (2 studies). Three studies found no significant difference for length of stay, positive surgical margins or number of positive lymph nodes. Two RCT's found no difference in complication rates between RARC and ORC at 30 to 90 days post-surgery, however 1 RCT found a quicker return to solid food for patients in the RARC group. One RCT found that RARC was non-inferior to ORC, with a second finding no difference in recurrence rates between methods. An RCT found no significant difference in HRQoL following

either method of radical cystectomy. One study found RARC to be more cost effective provided it could prevent over 70% of transfusions compared to ORC. A topic expert highlighted that the lower complication rates and standardisation of elective care were the key benefits of RARC compared to ORC.

Recommendations 1.5.4 – 1.5.6 state to offer radical cystectomy but do not specify which method should be used, allowing flexibility. The evidence found at this surveillance review indicated a number of benefits to RARC with improved patient outcomes, however it has an increased operative cost and operative time. An ongoing trial and a Cochrane protocol are being monitored in this area and as such may provide further evidence in the future. There is interventional procedures guidance on laparoscopic cystectomy (IPG287) which highlights that the procedure “may be performed with robotic assistance”. These recommendations should not be updated at this time.

Hyperbaric oxygenation therapy

Hyperbaric oxygenation therapy was not found to improve bladder cancer outcomes and was associated with adverse events. Hyperbaric oxygenation is not currently included in the recommendations for NG2, which is supported by the evidence found at this surveillance review.

Adjuvant chemotherapy

Adjuvant chemotherapy as suggested by a topic expert is included in recommendations 1.5.2 and 1.5.7. No evidence was identified through the surveillance to suggest changing these recommendations at this time.

New evidence is unlikely to change guideline recommendations.

Follow-up after treatment for muscle-invasive bladder cancer

Recommendations in this section of the guideline

- 1.6.1 Offer follow-up after radical cystectomy or radical radiotherapy.
- 1.6.2 After radical cystectomy consider using a follow-up protocol that consists of:
- monitoring of the upper tracts for hydronephrosis, stones and cancer using imaging and glomerular filtration rate (GFR) estimation at least annually **and**
 - monitoring for local and distant recurrence using CT of the abdomen, pelvis and chest, carried out together with other planned CT imaging if possible, 6, 12 and 24 months after radical cystectomy **and**
 - monitoring for metabolic acidosis and B12 and folate deficiency at least annually **and**
 - for men with a defunctioned urethra, urethral washing for cytology and/or urethroscopy annually for 5 years to detect urethral recurrence.
- 1.6.3 After radical radiotherapy consider using a follow-up protocol that includes all of the following:
- rigid cystoscopy 3 months after radiotherapy has been completed, followed by either rigid or flexible cystoscopy:
 - every 3 months for the first 2 years **then**
 - every 6 months for the next 2 years **then**
 - every year thereafter, according to clinical judgement and the person's preference
 - upper-tract imaging every year for 5 years
 - monitoring for local and distant recurrence using CT of the abdomen, pelvis and chest, carried out with other planned CT imaging if possible, 6, 12 and 24 months after radical radiotherapy has finished.
- 1.6.4 See [recommendation 1.2.1](#) on the use of urinary biomarkers for follow-up after treatment for bladder cancer.

Surveillance proposal

No new information was identified at any surveillance review.

This section of the guideline should not be updated

Managing locally advanced or metastatic muscle-invasive bladder cancer

Recommendations in this section of the guideline

First-line chemotherapy

- 1.7.1 Discuss the role of first-line chemotherapy with people who have locally advanced or metastatic bladder cancer. Include in your discussion:
- prognosis of their cancer and
 - advantages and disadvantages of the treatment options, including best supportive care.
- 1.7.2 Offer a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine, or accelerated [high-dose] methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] in combination with granulocyte-colony stimulating factor [G-CSF]) to people with locally advanced or metastatic urothelial bladder cancer who are otherwise physically fit (have an [Eastern Cooperative Oncology Group \[ECOG\] performance status](#) of 0 or 1) and have adequate renal function (typically defined as a glomerular filtration rate [GFR] of 60 ml/min/1.73 m² or more).
- 1.7.3 Offer carboplatin in combination with gemcitabine* to people with locally advanced or metastatic urothelial bladder cancer with an ECOG performance status of 0–2 if a cisplatin-based chemotherapy regimen is unsuitable, for example, because of ECOG performance status, inadequate renal function (typically defined as a GFR of less than 60 ml/min/1.73 m²) or comorbidity. Assess and discuss the risks and benefits with the person.
- 1.7.4 For people having first-line chemotherapy for locally advanced or metastatic bladder cancer:
- carry out regular clinical and radiological monitoring **and**
 - actively manage symptoms of disease and treatment-related toxicity **and**
 - stop first-line chemotherapy if there is excessive toxicity or disease progression.

Second-line chemotherapy

- 1.7.5 Discuss second-line chemotherapy with people who have locally advanced or metastatic bladder cancer. Include in your discussion:

- the prognosis of their cancer
 - advantages and disadvantages of treatment options, including best supportive care.
- 1.7.6 Consider second-line chemotherapy with gemcitabine in combination with cisplatin, or accelerated (high-dose) MVAC in combination with G-CSF for people with incurable locally advanced or metastatic urothelial bladder cancer whose condition has progressed after first-line chemotherapy if:
- their renal function is adequate (typically defined as a GFR of 60 ml/min/1.73 m² or more) **and**
 - they are otherwise physically fit (have an ECOG performance status of 0 or 1).
- 1.7.7 Consider second-line chemotherapy with carboplatin in combination with paclitaxel^[3] or gemcitabine in combination with paclitaxel** for people with incurable locally advanced or metastatic urothelial bladder cancer for whom cisplatin-based chemotherapy is not suitable, or who choose not to have it.
- 1.7.8 For recommendations on vinflunine as second-line chemotherapy for people with incurable locally advanced or metastatic urothelial bladder cancer, see NICE's technology appraisal guidance on [vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract](#).
- 1.7.9 For people having second-line chemotherapy for locally advanced or metastatic bladder cancer:
- carry out regular clinical and radiological monitoring **and**
 - actively manage symptoms of disease and treatment-related toxicity **and**
 - stop second-line chemotherapy if there is excessive toxicity or disease progression.

Managing symptoms of locally advanced or metastatic bladder cancer

Bladder symptoms

- 1.7.10 Offer palliative hypofractionated radiotherapy to people with symptoms of haematuria, dysuria, urinary frequency or nocturia caused by advanced bladder cancer that is unsuitable for potentially curative treatment.

Loin pain and symptoms of renal failure

- 1.7.11 Discuss treatment options with people who have locally advanced or metastatic bladder cancer with ureteric obstruction. Include in your discussion:
- prognosis of their cancer **and**
 - advantages and disadvantages of the treatment options, including best supportive care.

- 1.7.12 Consider percutaneous nephrostomy or retrograde stenting (if technically feasible) for people with locally advanced or metastatic bladder cancer and ureteric obstruction who need treatment to relieve pain, treat acute kidney injury or improve renal function before further treatment.
- 1.7.13 If facilities for percutaneous nephrostomy or retrograde stenting are not available at the local hospital, or if these procedures are unsuccessful, discuss the options with a specialist urology multidisciplinary team for people with bladder cancer and ureteric obstruction.

Intractable bleeding

- 1.7.14 Evaluate the cause of intractable bleeding with the local urology team.
- 1.7.15 Consider hypofractionated radiotherapy or embolisation for people with intractable bleeding caused by incurable bladder cancer.
- 1.7.16 If a person has intractable bleeding caused by bladder cancer and radiotherapy or embolisation are not suitable treatments, discuss further management with a specialist urology multidisciplinary team.

Pelvic pain

- 1.7.17 Evaluate the cause of pelvic pain with the local urology team.
- 1.7.18 Consider, in addition to best supportive care, 1 or more of the following to treat pelvic pain caused by incurable bladder cancer:
- hypofractionated radiotherapy if the person has not had pelvic radiotherapy
 - nerve block
 - palliative chemotherapy.

*Although this use is common in UK clinical practice, at the time of publication (February 2015), carboplatin in combination with gemcitabine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

**Although this use is common in UK clinical practice, at the time of publication (February 2015), gemcitabine in combination with paclitaxel did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

Surveillance proposal

This section of the guideline should not be updated.

Editorial amendments

We will add a cross referral to the bladder cancer pathway from recommendations 1.7.7 and 1.7.8 to highlight the new technology appraisals that are available.

Managing locally advanced or metastatic muscle-invasive bladder cancer

2018 surveillance summary

A Cochrane review(29) of 1 trial (n=542 participants) assessed the effects of pembrolizumab monotherapy compared to chemotherapy for treatment of advanced urothelial carcinoma. The results indicate that pembrolizumab probably reduces the risk of death from any cause, and may slightly improve the quality of life. In terms of secondary outcomes, pembrolizumab significantly improved treatment response and may reduce adverse events. However it had little or no effect on disease progression or treatment-related mortality. The review states that the trial was sponsored by the producer of pembrolizumab.

Intelligence gathering

One topic expert highlighted immunotherapy for advanced disease as an area where ongoing research may be available and referred to 2 technology appraisals:

- TA519- Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy
- TA522 - Pembrolizumab for untreated PD-L1-positive locally advanced or

metastatic urothelial cancer when cisplatin is unsuitable

An ongoing trial was identified through intelligence gathering which is investigating the optimal dose of [SGI-110](#) when given in combination with gemcitabine for the treatment of bladder cancer. This study will be monitored and assessed for impact once available.

Impact statement

A Cochrane review found that pembrolizumab may reduce mortality and improve QoL, treatment response and adverse events compared to chemotherapy. Immunotherapy for metastatic disease was also highlighted as a potential area for updating by a topic expert. Pembrolizumab/immunotherapy are not mentioned in the recommendations for NG2. Pembrolizumab is currently limited to the cancer drugs fund. Further information is found in TA519- Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy and TA522 - Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable which are linked in the [bladder cancer pathway](#).

New evidence is unlikely to change guideline recommendation

Specialist palliative care for people with incurable bladder cancer

Recommendations in this section of the guideline

- 1.8.1 A member of the treating team should offer people with incurable bladder cancer a sensitive explanation that their disease cannot be cured and refer them to the urology multidisciplinary team.
- 1.8.2 Tell the primary care team that the person has been given a diagnosis of incurable bladder cancer within 24 hours of telling the person.
- 1.8.3 A member of the urology multidisciplinary team should discuss the prognosis and management options with people with incurable bladder cancer.
- 1.8.4 Discuss palliative care services with people with incurable bladder cancer and, if needed and they agree, refer them to a specialist palliative care team (for more information, see [recommendation 1.1.4](#) on holistic needs assessment and NICE's guidelines on [improving supportive and palliative care for adults with cancer](#) and [improving outcomes in urological cancers](#)).
- 1.8.5 Offer people with symptomatic incurable bladder cancer access to a urological team with the full range of options for managing symptoms.

Surveillance proposal

No new information was identified at any surveillance review.

This section of the guideline should not be updated.

Research recommendations

What are the causative and contributory factors underlying the persistently very low levels of reported patient satisfaction for bladder cancer?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

Is primary radical cystectomy more effective than primary intravesical BCG in [high-risk](#) non-muscle-invasive bladder cancer, in terms of quality of life and cancer-specific outcomes?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

In people with high-risk non-muscle-invasive bladder cancer, are these follow-up regimens equally effective in terms of identification of progression, cost-effectiveness and health-related quality of life?

- Cystoscopic follow-up at 3, 6, 12, 18, 24, 36 and 48 months, and then annually, interspersed with non-invasive urinary tests.
- Cystoscopic follow-up at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42 and 48 months, and then annually thereafter.

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

In patients with muscle-invasive bladder cancer suitable for radical treatment, does the use of biomarkers enable patients to select more effective treatment, and improve their outcomes, compared with treatment selected without biomarkers?

Summary of findings

New evidence was found relating to urinary biomarkers for the detection of bladder cancer, however our searches did not include biomarkers for treatment optimisation. We found 1 ongoing study relating

to targeted therapy based on biomarker profiles which will be assessed for relevance once available. ([An adaptive multi-arm phase II trial of maintenance targeted therapy after chemotherapy in metastatic urothelial cancer](#)).

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

Is symptom-based review as effective as scheduled follow-up for people treated with radical cystectomy or radical radiotherapy for organ-confined, muscle-invasive bladder cancer? Outcomes of interest are overall survival, health-related quality of life, resource use and cost.

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

In people with newly diagnosed bladder cancer who smoke, is an enhanced smoking cessation programme more effective than a standard programme in terms of bladder cancer recurrence, progression and overall survival

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

In people with suspected bladder cancer does using photodynamic diagnosis instead of narrow-band imaging improve outcomes for bladder cancer recurrence, progression or overall survival?

Summary of findings

No new published evidence relevant to the research recommendation was found. One ongoing study was highlighted by topic experts and identified in our initial intelligence gathering that will be tracked and assessed for relevance once available: [Photodynamic versus white light-guided treatment of non-muscle invasive bladder cancer](#).

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

Do biomarkers or novel cystoscopic technologies improve outcomes in patients undergoing surveillance after a diagnosis of bladder cancer compared to standard cystoscopic surveillance? Outcomes of interest are HRQoL, progression to MIBC, cystectomy rate, and bladder cancer mortality.

Summary of findings

We searched for new evidence regarding [urinary biomarkers](#) for both initial and recurrence detection of bladder cancer. The sensitivity results were mixed and a topic expert indicated that they were not strong enough for clinical use compared to cystoscopy.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

Does the addition of biomarkers or cytology to cystoscopy improve outcomes in patients undergoing surveillance after receiving BCG therapy for bladder cancer? Outcomes of interest are HRQoL, progression to MIBC, cystectomy, and bladder cancer death.

Summary of findings

The focused search on urinary biomarkers found evidence relating to detection of bladder cancer compared to cystoscopy. No new evidence or ongoing trials were identified that examined the use of biomarkers as an addition to cystoscopy.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

In people with exclusively low-risk bladder cancer who experience recurrence does the addition of biopsy to fulguration or laser treatment improve progression, recurrence, morbidity and quality of life?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

In people who cannot tolerate BCG or with persistent or recurrent disease after BCG, or who are not suitable for radical cystectomy is novel intravesical therapy or radiotherapy more effective than the current standard of care (for example intravesical mitomycin C) in terms of recurrence, progression, survival and quality of life?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

In people who cannot tolerate BCG or with persistent or recurrent disease after BCG, or who are not suitable for radical cystectomy is novel intravesical therapy or radiotherapy more effective than the current standard of care (for example intravesical mitomycin C) in terms of recurrence, progression, survival and quality of life?

Summary of findings

No new published evidence relevant to the research recommendation was found. An ongoing trial has been identified which will be tracked and assessed once available, [Intravesical bacillus Calmette-Guérin versus mitomycin C for Ta and T1 bladder cancer](#).

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

Which interventions are effective in preventing or treating symptoms of bladder toxicity in people having BCG or radiation? A randomised trial should measure toxicity, quality of life, bladder cancer recurrence and progression.

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

In which people with muscle-invasive bladder cancer does neo-adjuvant chemotherapy improve outcomes?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

In patients with muscle-invasive bladder cancer suitable for radical treatment, does the use of biomarkers enable patients to select more effective treatment, and improve their outcomes compared with treatment selected without biomarkers?

Summary of findings

Although evidence was found for biomarkers, this was focused on urinary biomarkers for the detection of new or recurrent bladder cancer and, as such, not relevant to this research recommendation.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

What is the quality of life (and other patient reported outcomes) of patients with muscle-invasive bladder cancer before, during and after radical treatment?

Summary of findings

Three trials had health-related quality of life as a secondary outcome for robotic compared to open cystectomy, however no difference between groups was seen. Several ongoing trials are being tracked where quality of life is a main or secondary outcome and results will be considered for impact on the guideline when available:

- [Health related quality of life after radical cystectomy](#)
- [Standard open radical cystectomy \(ORC\) versus robotically assisted radical cystectomy \(RARC\)](#)
- [Replacement of a surgical procedure called transurethral resection of bladder tumour with a painless imaging procedure called magnetic resonance imaging in patients with muscle invasive bladder cancer](#)
- [Quality of life after bladder cancer \(Q-ABC\)](#)

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

Can biomarkers accurately predict the effectiveness of radiosensitisers (for example mitomycin C and 5-FU or carbogen and nicotinamide) in muscle-invasive bladder cancer treated with radical radiotherapy?

Summary of findings

Although evidence was found for biomarkers, this was focused on urinary biomarkers for the detection of new or recurrent bladder cancer and as such not relevant to this research recommendation.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

In patients with incurable locally advanced or metastatic bladder cancer after first-line chemotherapy what is the most effective second-line therapy (including single agent, combination therapy, novel agents or best supportive care).

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance proposal

This research recommendation will be considered again at the next surveillance point.

References

1. Fu L, Wang R, Yin L, Zhang P, Tian Y, Niu M (2016) Nuclear matrix protein 22 (NMP22) test in the diagnosis of bladder cancer: A meta-analysis. *International Journal of Clinical and Experimental Medicine* 9(5):7965–75

2. Dahmcke CM, Steven KE, Larsen LK, Poulsen AL, Abdul-AI A, Dahl C, et al. (2016) A Prospective Blinded Evaluation of Urine-DNA Testing for Detection of Urothelial Bladder Carcinoma in Patients with Gross Hematuria. *European Urology* 70(6):916–9
3. Ribal MJ, Mengual L, Lozano JJ, Ingelmo-Torres M, Palou J, Rodriguez-Faba O, et al. (2016) Gene expression test for the non-invasive diagnosis of bladder cancer: A prospective, blinded, international and multicenter validation study. *European Journal of Cancer* 54:131–8
4. Chou R, Gore JL, Buckley D, Fu R, Gustafson K, Griffin JC, et al. (2015) Urinary Biomarkers for Diagnosis of Bladder Cancer: A Systematic Review and Meta-analysis. *Annals of Internal Medicine* 163(12):922–31
5. Vadasz Z, Rubinstein J, Bejar J, Sheffer H, Halachmi S (2018) Overexpression of semaphorin 3A in patients with urothelial cancer. *Urologic Oncology* 36(4):161.e1-161.e6
6. Tinawi-Aljundi R, King L, Knuth ST, Gildea M, Ng C, Kahl J, et al. (2015) One-year monitoring of an oligonucleotide fluorescence in situ hybridization probe panel laboratory-developed test for bladder cancer detection. *Research and Reports in Urology* 7:49–55
7. Todenhofer T, Hennenlotter J, Esser M, Mohrhardt S, Aufderklamm S, Bottge J, et al. (2014) Stepwise application of urine markers to detect tumor recurrence in patients undergoing surveillance for non-muscle-invasive bladder cancer. *Disease Markers* 2014:973406
8. Pichler R, Tulchiner G, Fritz J, Schaefer G, Horninger W, Heidegger I (2017) Urinary UBC Rapid and NMP22 Test for Bladder Cancer Surveillance in Comparison to Urinary Cytology: Results from a Prospective Single-Center Study. *International Journal of Medical Sciences* 14(9):811–9
9. Su SF, de Castro Abreu AL, Chihara Y, Tsai Y, Andreu-Vieyra C, Daneshmand S, et al. (2014) A panel of three markers hyper- and hypomethylated in urine sediments accurately predicts bladder cancer recurrence. *Clinical Cancer Research* 20(7):1978–89
10. Sathianathen NJ, Butaney M, Weight CJ, Kumar R, Konety BR (2018) Urinary Biomarkers in the Evaluation of Primary Hematuria: A Systematic Review and Meta-Analysis. *Bladder Cancer* 4(4):353–63
11. Jung JH, Gudeloglu A, Kiziloz H, Kuntz GM, Miller A, Konety BR, et al. (2017) Intravesical electromotive drug administration for non-muscle invasive bladder cancer. *Cochrane Database of Systematic Reviews* (9)
12. Shepherd ARH, Shepherd E, Brook NR (2017) Intravesical Bacillus Calmette-Guérin with interferon-α versus intravesical Bacillus Calmette-Guérin for treating non-muscle-invasive bladder cancer. *Cochrane Database of Systematic Reviews* (3)
13. Fonseka T, Ahmed K, Froghi S, Khan SA, Dasgupta P, Shamim Khan M (2015) Comparing robotic, laparoscopic and open cystectomy: a systematic review and meta-analysis. *Archivio Italiano di Urologia, Andrologia* 87(1):41–8
14. Ishii H, Rai BP, Stolzenburg JU, Bose P, Chlosta PL, Somani BK, et al. (2014) Robotic or open radical cystectomy, which is safer? A systematic review and meta-analysis of comparative studies. *Journal of Endourology* 28(10):1215–23
15. Lauridsen S V, Tonnesen H, Jensen BT, Neuner B, Thind P, Thomsen T (2017)

- Complications and health-related quality of life after robot-assisted versus open radical cystectomy: a systematic review and meta-analysis of four RCTs. *Systematic Reviews* 6(1):150
16. Novara G, Catto JW, Wilson T, Annerstedt M, Chan K, Murphy DG, et al. (2015) Systematic review and cumulative analysis of perioperative outcomes and complications after robot-assisted radical cystectomy. *European Urology* 67(3):376–401
 17. Shen Z, Sun Z (2016) Systematic review and meta-analysis of randomised trials of perioperative outcomes comparing robot-assisted versus open radical cystectomy. *BMC Urology* 16(1)
 18. Tan WS, Khetrapal P, Tan WP, Rodney S, Chau M, Kelly JD (2016) Robotic Assisted Radical Cystectomy with Extracorporeal Urinary Diversion Does Not Show a Benefit over Open Radical Cystectomy: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *PLoS ONE [Electronic Resource]* 11(11):e0166221
 19. Tang K, Xia D, Li H, Guan W, Guo X, Hu Z, et al. (2014) Robotic vs. open radical cystectomy in bladder cancer: A systematic review and meta-analysis. *European Journal of Surgical Oncology* 40(11):1399–411
 20. Xia L, Wang X, Xu T, Zhang X, Zhu Z, Qin L, et al. (2015) Robotic versus open radical cystectomy: an updated systematic review and meta-analysis. *PLoS ONE [Electronic Resource]* 10(3):e0121032
 21. Tang JQ, Zhao Z, Liang Y, Liao G (2018) Robotic-assisted versus open radical cystectomy in bladder cancer: A meta-analysis of four randomized controlled trails. *The International Journal Of Medical Robotics + Computer Assisted Surgery: MRCAS* 14(1)
 22. Bochner BH, Dalbagni G, Sjoberg DD, Silberstein J, Keren Paz GE, Donat SM, et al. (2015) Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial. *European Urology* 67(6):1042–50
 23. Bochner B, Dalbagni G, Marzouk K, Sjoberg D, Lee J, Donat S, et al. (2018) Randomized Trial Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: oncologic Outcomes. *European urology* (no pagination)
 24. Khan MS, Gan C, Ahmed K, Ismail AF, Watkins J, Summers JA, et al. (2016) A Single-centre Early Phase Randomised Controlled Three-arm Trial of Open, Robotic, and Laparoscopic Radical Cystectomy (CORAL). *European Urology* 69(4):613–21
 25. Messer JC, Punnen S, Fitzgerald J, Svatek R, Parekh DJ (2014) Health-related quality of life from a prospective randomised clinical trial of robot-assisted laparoscopic vs open radical cystectomy. *BJU International* 114(6):896–902
 26. Parekh D, Reis I, Castle E, Gonzalgo M, Woods M, Svatek R, et al. (2018) Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. *Lancet* 391(10139):2525–36
 27. Kukreja JB, Metcalfe MJ, Qiao W, Kamat AM, Dinney CPN, Navai N (2018) Cost-Effectiveness of Robot-assisted Radical Cystectomy Using a Propensity-matched Cohort. *European Urology Focus* 19:19

28. Bennett MH, Feldmeier J, Smee R, Milross C (2018) Hyperbaric oxygenation for tumour sensitisation to radiotherapy. Cochrane Database of Systematic Reviews (4)
29. Narayan V, Kahlmeyer A, Dahm P, Skoetz N, Risk MC, Bongiorno C, et al. (2018) Pembrolizumab monotherapy versus chemotherapy for treatment of advanced urothelial carcinoma with disease progression during or following platinum-containing chemotherapy. A Cochrane Rapid Review. Cochrane Database of Systematic Reviews (7)

© NICE 2019. All rights reserved. Subject to [Notice of rights](#).