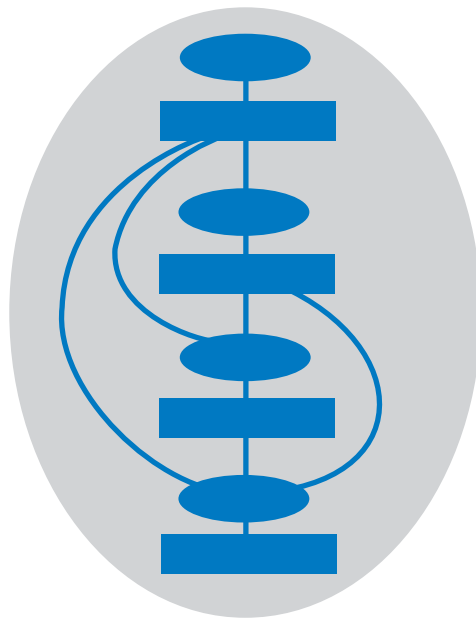


Guidance for Commissioning Cancer Services

Improving Outcomes in Urological Cancers

The Research Evidence



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This document is published by CRD on behalf of the National Cancer Guidance Steering Group. It is the companion document to *Improving Outcomes in Urological Cancers: The Manual* published by NICE, and is part of the Improving Outcomes in Cancer Series.

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Introduction

This document complements and is designed to be read alongside *Guidance for Commissioning Cancer Services – Improving Outcomes in Urological Cancers: The Manual*. It provides a condensed version of reviews of the research evidence relevant to the recommendations made in the manual. As with previous documents in the series, the topic areas are dealt with in the same order as in the manual to facilitate cross-referencing.

This document presents a summary of a series of reviews commissioned and conducted by researchers from the NHS Centre for Reviews and Dissemination (CRD). Reviews were commissioned from Professor Malcolm Mason, Velindre NHS Trust, and Professor Irene Higgins, King’s College School of Medicine and Dentistry (see Appendix 3).

Table 1: Grading of evidence

Grade	Evidence	
	Diagnosis	Treatment
I	Systematic review of at least level II (below) studies	
II	A blind comparison with reference standard among an appropriate broadly defined consecutive sample of patients	
III	Systematic review of poorer than level II (above) studies	
IV	Any one of the following	<ul style="list-style-type: none"> ➤ Narrow population spectrum. ➤ Differential use of reference standard.
V	Any two of the following	
VI	Any three or four of the following.	<ul style="list-style-type: none"> ➤ Reference standard not blind. ➤ Case control study design
VII	Expert opinion, consensus	

As part of the systematic review process, thorough searches were carried out for each review question. Where appropriate, strategies were limited by methodology or date. Searches were conducted for each question on a number of electronic databases. The reference lists of studies identified through the search were used to retrieve other potentially relevant studies. Additional material was provided by referees and experts in the various fields. The search process was undertaken by Kate Misso (CRD) and Bernadette Coles (Velindre Trust). Full details of the searches and strategies used are available from CRD (Telephone 01904 433707; E-mail nhscrd-info@york.ac.uk).

Studies were included in the reviews according to pre-defined criteria. Quality assessment of the studies was conducted using the relevant schemes set out in guidance on undertaking systematic reviews produced by CRD. The studies were

graded using agreed criteria as outlined in Table 1, which is derived from the CRD guidance.^a This grading broadly corresponds with the Clinical Outcomes Group categories of evidence for use in the writing of clinical practice guidelines, where A = I or II, B = III, IV, V or VI and C = VII.^b

Most of the published research on urological cancers focuses on clinical evaluation of treatment; relatively little direct research has been carried out on the organisation and delivery of services. In addition, for many service delivery issues, RCTs (categorised here as the highest quality evidence) are not feasible. Therefore, research designs which are regarded as of relatively poor quality for evaluating a clinical intervention may be the most reliable available for assessing the effectiveness of service delivery.

The nature of the evidence concerning each question is described and the results summarised along with tables of studies giving fuller details of the research.

Two complementary pieces of research were commissioned; one to elicit patients' views about urological cancer services and the second to examine the cost impact of the recommendations. The National Cancer Alliance, Oxford, was commissioned to undertake a small-scale exercise to enable urological cancer patients to input their views, knowledge and experience into the development of the guidance (see Appendix 1). The School of Health and Related Research at the University of Sheffield was commissioned to examine the potential cost implications of the reconfiguration of services into cancer units and centres recommended in the guidance (see Appendix 2).

This document was prepared by Adrian Flynn, Alison Eastwood and Jos Kleijnen at the NHS Centre for Reviews and Dissemination.

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- a NHS Centre for Reviews and Dissemination. *Report 4 - Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews*. 2 ed. York: NHS Centre for Reviews and Dissemination, University of York, 2001.
- b Mann T. *Clinical Guidelines: using clinical guidelines to improve patient care within the NHS*. London: NHS Executive, 1996.

The Urological Cancer Network and Multidisciplinary Teams

The Questions

- a) In urological oncology, are patient outcomes influenced by any of the following:
- the volume of urological cancer-related interventions performed by a clinician
 - the volume of urological cancer-related interventions performed at a hospital
 - the specialisation of those professionals treating the patients
 - the centralisation of the oncology service?
- b) Do multidisciplinary teams (MDTs) working in urological oncology improve patients outcomes by developing the expertise of professionals or by improving communication between and within the primary, urological and oncological areas of the health service?

The Nature of the Research Evidence

a) Volume and specialisation

Three systematic reviews were identified which examined the relationship between the volume and quality of treatments offered to patients with urological cancers, i.e. the concentration of services¹⁻³ (Table 1.1a). However, one of these³ is subsumed by the more recent reviews.^{1,2} Both reviews include surgery for prostate cancer; one also includes treatments for testicular cancer.¹

A further systematic review investigated whether patients outcomes were improved if treated by physicians/centres who maintained a special interest in a particular disease or treatment, i.e. the specialisation of services.⁴ This review included patients with prostate, bladder and testicular cancers (Table 1.1a).

The reviews were well conducted. Each review assessed the quality of included studies. One included only studies which had taken account of co-morbidity¹ while another awarded grades to studies to demonstrate the quality of the study.² Concentration and specialisation of services often accompany each other. When this is the case, it is sometimes difficult to discern whether the concentration of services to high volume providers or the specialisation of treatments to experienced professionals has the greater influence on altered clinical outcomes. It is a limitation of much of the research that this question is not fully explored.

Six additional primary studies were located⁵⁻¹⁰ (Table 1.1b). Data from a national cancer register were analysed to assess the relationship between mortality following treatment for testicular cancer and hospital volume.⁵ A retrospective analysis of a case series investigated the relationship between urologists' case loads and their use of diagnostic tests in the management of prostate cancer.⁶ A Swedish and Norwegian trial⁷ assessed the treatment of men with Non-seminoma Germ Cell Tumour (NSGCT) and examined the levels of skill in the area of clinical staging of patients with respect to the volume of patients treated.

Additionally, a registry-based study of patients with bladder cancer measured survival in relation to the type of hospital at which the patient had his or her treatment.⁸

Two analyses of centralised or specialised pathology for urological cancer were found. One addressed the benefit of central review of slides by a cancer centre in testicular cancer management;⁹ the second compared fine needle prostate biopsy samples from local community hospitals and a high volume academic setting.¹⁰

No research was located which addressed issues of concentration of services in the care of patients diagnosed with cancer of the kidney or cancer of the penis.

b) Multidisciplinary teams

A review addressing issues of specialisation was identified.⁴ It included registry data from the Republic of Ireland on the influence of urologists and oncologists on survival in testicular cancer patients (Table 1.2a).

A survey of patients with prostate cancer treated during one year at a multidisciplinary clinic assessed the patients' perceptions of their treatment¹¹ (Table 1.2b).

Summary of the Research Evidence

a) Volume and specialisation

One systematic review examined the relationship between the number of cancer patients treated and the quality of treatment they received.¹ The review was based on four studies, including one from the UK. It found a clear relationship between increased volume and improved quality of care as measured by greater survival and lower relative risk of death for seminoma and NSGCT.

In addition, high volume hospitals were more likely to treat men with testicular cancer according to predefined protocols than low volume hospitals (97% against 61%). Evidence relating to the mortality rates in radical prostatectomy was also reviewed.¹ Analysis of data from US and Canadian registers found that low volume hospitals had significantly higher 30 day mortality. The US data also found higher serious complication rates and more re-admissions in patients treated at low volume hospitals.

A second systematic review² addressed the same question and reported the same registry data from the USA and additional data from an insurance database. Regionalisation of the prostatectomy service was deemed not justified partially

because of comparisons of data returned by hospitals to the registry in successive years. Despite an increase in volume over time, these hospitals failed to deliver a commensurate improvement in patient outcomes.

A systematic review addressed whether patients had better outcomes if treated by specialised physicians/centres.⁴ Evidence from Finland suggested a reduction in mortality of men with prostate cancer treated at a university medical centre when compared with men treated in local settings. When evidence from registry data from the South East and South West Thames regions was reviewed, the employment grade of the surgeon (i.e. consultant, registrar etc) operating on patients with bladder cancer had no effect on the prognosis of the patient. Scant information was given about this study in the review and no attempt is made to explain the differences between this finding and the finding in other diagnostic categories.

The appropriateness of the diagnostic interventions requested by urologists seeing high, medium and low numbers of men with prostate cancer has been examined.⁶ Urologists who saw larger numbers of men requested bone scans for men with low PSA levels less often than did the remaining urologists. High and medium volume urologists requested comparable numbers of CT scans, irrespective of PSA. Low volume urologists however ordered CT scans for a noticeably larger proportion of men. However, only ten urologists were involved: two, two and six in the high, medium and low volume categories respectively. While these differences may be significant, the small population in the study renders extrapolation problematic.

Analysis of registry data from Scotland about 391 patients, treated for NSGCT between 1983 and 1988, showed that 55% of all patients were treated at one centre. The hospital had the lowest disease specific and all cause mortality (survival = 94.2%).⁵ The centre with the highest mortality figures had the lowest number of patients (survival = 70.2%, $\chi^2 = 14.46$, 2 d.f. $p < 006$). The lowest volume hospital had the highest proportion (20% compared with 1% at the highest volume hospital) of patients whose treatment was judged to have been sub-optimal, when factors outside of the hospital's control were excluded.

A collaborative Scandinavian study assessed the management of patients with NSGCT in Norway and Sweden.⁷ Trialists assessed the skills of clinicians in assigning the correct clinical stage. In the study, the rate at which patients were accrued into the project was used as a proxy for the volume of treatments delivered by the hospital. Using the pathological stage as the gold standard, the specificity, sensitivity and overall accuracy was calculated for hospitals in the three volume categories.⁷ While the highest accrual hospital had significantly better sensitivity, it was significantly worse in terms of specificity. The overall accuracy was comparable across all three groups (77%, 74% and 74% for low, medium and high accrual hospitals). The trialists conclude that there is no difference between clinicians working in high, medium and low accrual hospitals in relation to their ability to adequately stage patients with NSGCT.⁷ Questions remain in relation to the use of the rate of accrual of study subjects as a proxy for overall patient volume in participating centres.

A retrospective analysis of data from a cancer registry in East Anglia addressed survival in patients with a number of cancers including bladder cancer.⁸ Hospitals were classified as either Group 1 hospitals (high volume hospitals with

radiotherapy and oncology departments) or Group 2 hospitals (low volume hospitals without radiotherapy and oncology departments). The hazard ratio comparing survival to five years after diagnosis with bladder cancer in Group 2 hospitals relative to Group 1 hospitals, adjusted for age, sex and TNM stage, was 1.09 (95% CI: 0.96 to 1.24).⁸ Varying volumes within the hospital groups had no significant effect on the hazard ratio however. The findings were independent of age. The authors reported that in one hospital, patients with bladder cancer were systematically understaged leading to inappropriate treatments and poorer than expected stage specific survival data. They postulated that this had no overall effect on pooled data but did not state if this hospital was in Group 1 or Group 2.

A prospective comparison of the reports issued at twelve referring hospitals and the reports issued at a cancer centre was conducted at Southampton.⁹ It included histo-pathological specimens sent to the cancer centre for review of a testicular cancer diagnosis between 1992 and 1997. 208 of the 220 specimens received in the time period were reviewed. Accuracy of diagnosis was investigated. Where a diagnosis was altered, any effect on the subsequent management of the patient was recorded. Twelve patients (6%) had a significant alteration of their diagnosis made after expert review. A total of eight patients (4%) had their management altered. Four patients had radiotherapy cancelled, two patients underwent additional surgery, one patient had additional chemotherapy and one patient had surgery brought forward. Four patients did not require any change in management despite the change in diagnosis. Reports from referring hospitals on specimens from 48 men with NSGCT (44%) did not mention vascular invasion. In the 59 cases where a definitive comment was made on vascular invasion, 12 were incorrect (20%).

A similar study from the US compared fine needle biopsy samples from local community hospitals with a high volume academic setting.¹⁰ Data on 499 patients who had a radical prostatectomy at an academic hospital were evaluated. A total of 390 had had biopsies in both their local community hospital and the academic setting. The authors assessed the correlation. Complete agreement was noted in 240 cases (62%) but one area of major difference was noted in the classification of Gleason grade 2 to 4 tumours. Local hospital pathologists had awarded this to 22% of the tumours (87 patients) but the high volume hospital awarded it in 1% (four patients).¹⁰ It is noteworthy that none of these patients were found to have grade 2 to 4 disease following review of their post prostatectomy histology report. Of all 499 patients who had both a fine needle biopsy and a radical prostatectomy in the academic hospital, the authors looked at the specialisation of the pathologist who reported on the specimen. In the cases of 82 men, (16%) reports were written by a specialist GU pathologist while the remaining 84% (417 cases) were reported by a general pathologist who did not specialise in GU pathology. The reports were compared with those given post prostatectomy. No advantage in having a pathological review conducted by a specialist GU pathologist was demonstrated. Agreement was 0.552 for the GU pathologist and 0.545 for the others. A weakness of this comparison is that the study does not clarify the number of GU and non-GU pathologists involved. Additionally it does not clarify whether the post prostatectomy report was written by a GU or non-GU pathologist.

Each study compares external with local reporting and both assume that the local report is correct.^{9,10} There is also an implied bias affecting the US study created by the high volume hospital biopsy being reported by the same staff of pathologists as report the post prostatectomy specimen.

Notwithstanding these potential biases, the greater accuracy of high volume pathologists conducting biopsy reporting in the US study and the small but important rate of diagnosis alterations in the British study taken together imply that specialist pathological knowledge has an effect on the patient's care. Neither study assess the effect in terms of true patient outcomes but the British study did assess the alteration in management which will have an effect on outcomes.

Conclusions

Evidence found, both from systematic reviews and from primary research studies, suggests that a concentration of an activity to a small number of professionals usually leads to an increase in the effectiveness of that intervention. This appeared true for both the treatment of prostate and testicular cancers and for the appropriate investigation of prostate cancer. Evidence in the area of bladder cancer does not support this premise however.

This improvement in outcomes may be owing to concentration of services to higher volume providers; alternatively it may be caused by the development of an increased skill base amongst medical, nursing, allied profession, managerial and support staff. The relative importance of these two mechanisms is unclear from the literature. Evidence suggests, however, that in any given service, increased through-put alone will not necessarily lead to an improvement in the quality of care offered to patients.

b) Multidisciplinary teams

A systematic review addressing whether patients had better outcomes if treated by specialised physicians/centres⁴ reported data from the Republic of Ireland which showed a statistically non-significant reduction in mortality from testicular cancers treated by specialists (urologists and oncologists). This trend appears to support the treatment of patients with these urological malignancies by professionals with the experience and interest in urological oncology.

A survey of men attending a university hospital based multidisciplinary genitourological oncology clinic in the USA assessed the views of those who were diagnosed with prostate cancer during one year.¹¹ In the clinic, medical oncologists, radiation oncologists and urologists were present. All patients were seen by a urologist, 41% of patients also consulted with a radiation oncologist and 5% consulted with a medical oncologist.

60% of patients had been referred to the clinic for a second opinion. Patients of the clinic were satisfied with the adequacy of the information given to them by the specialist(s) seen in 91% of cases while 96% of patients were able to decide on the course of treatment best for them after their consultation.

Conclusions

There is a relative lack of evidence that specifically assesses the effect of the MDT-working by professionals, as apart from the effect of increased patient numbers. However, the evidence assessed supports the belief that specialist care offers improved patient outcomes.

In particular, in urological oncology both the patients perception of care and rates of survival were improved following consultation with a specialist oncologist or urologist.

Table 1.1a: Concentration and specialisation of services in the treatment of urological malignancies: systematic reviews

Study Country Grade	Aims	Included studies	Methods	Outcomes	Results	Comments
Grilli, 1998. ⁴ Italy III	To assess the impact of specialisation on processes and outcomes of care for cancer patients.	<p><i>Participants</i> Patients with urological cancers including cancers of the prostate and bladder.</p> <p><i>Interventions</i> Prostate – Treatment for prostate cancer in a university hospital/non-university hospital; Bladder – Operation performed by a specialist or trainee surgeon.</p> <p><i>Design</i> Systematic review reporting on a population-based study of prostate patients in Finland and a retrospective cohort study of English men with bladder cancer.</p>	<p><i>Period</i> 1980 to 1998.</p> <p><i>Adjustment for confounding variables</i> Pooling was only conducted if the adjustment was adequately performed.</p>	<p><i>Prostate cancer</i> Mortality.</p> <p><i>Bladder cancer</i> Duration of survival.</p>	<p><i>Prostate cancer</i> Improved mortality for prostate patients treated in teaching hospitals in Finland (volume is unspecified).</p> <p><i>Bladder cancer</i> Non-statistically significant mortality improvement in bladder cancer patients operated on by a specialist urological surgeon in South East England (specialism of physician used as proxy of higher volume).</p>	<p>The similarity of the Finish health service and the NHS facilitates transfer of the findings on prostate cancer to the UK.</p> <p>The bladder study was conducted in the UK and so can easily be applied to the NHS as a whole.</p> <p>The review is comprehensive and well conducted.</p> <p>There is a small section dealing with urological cancers but details of the individual studies is not comprehensive.</p> <p>Data were presented in graphical format with little accompanying text.</p> <p><i>Inclusion criteria</i> Good</p> <p><i>Literature search</i> Fair</p> <p><i>Quality assessment</i> Fair</p> <p><i>Study details</i> Fair</p> <p><i>Pooling and/or synthesis</i> Fair</p>





Study Country Grade	Aims	Included studies	Methods	Outcomes	Results	Comments
Hillner, 2000. ¹ USA III	To assess whether hospital or physician volume or speciality affects the outcome of cancer care.	<p><i>Participants</i> Patients with variety of cancers, including a section on prostate and testicular cancer.</p> <p><i>Interventions</i> Radical prostatectomy, radiotherapy and chemotherapy for testicular cancer.</p> <p><i>Design</i> Systematic review reporting on retrospective analyses of insurance claims for prostatectomy from the US and from Canada and on four studies describing experience with testicular tumours – two population-based studies and two re-analyses of information from separate trial data.</p>	<p><i>Period</i> 1988 to 1999.</p> <p><i>Adjustment for confounding variables</i> Only studies which adjusted for demographic factors and/or co-morbidity were included in the review.</p>	<p><i>Prostate Cancer</i> 30 day mortality. Complications rates. Readmission rates.</p> <p><i>Testicular cancer</i> Survival rates (three and four year data) and relative risk of death.</p>	<p><i>Prostate cancer</i> One study (n = 101,604) found a clear association between improving outcomes and increasing hospital volume, analysed by quartile (low volume defined as less than 39 prostatectomies per year, medium low as 39 to 74, medium high as 75 to 140 and high as greater than 140 per year). Smaller hospitals had higher 30 day mortality, readmission within 30 days rates and higher complication rates. The second study (n = 4,997) found a lower 30 day mortality rate at academic rather than community centres (academic status used as proxy for higher volume).</p> <p><i>Testicular cancer</i> One US population-based study (n = 305) found those patients treated in a large academic hospital had lower mortality, irrespective of disease stage (academic status used as proxy for higher volume). Similar results were seen in two re-analyses of Swedish/Norwegian (n = 193) and European (n = 380) trial data, as well as in a Scottish registry-based study (n = 429) (cut-off points are not defined).</p>	<p>One of the studies pertaining to prostate cancer was concerned with overall volume, the other with hospital categories.</p> <p>Both prostate studies originate in North America and are based on insurance claims so applicability to the NHS is uncertain.</p> <p>Testicular information is consistent despite studies being based on the US, the UK and a number of other European countries; application of the findings to the NHS seems justified.</p> <p>Only a small part of the review was concerned with prostate or testicular cancers.</p> <p>Details of the search strategy and question were given but information on the process, such as whether more than one person extracted data, is not given. The narrative is well written but not comprehensive.</p> <p><i>Inclusion criteria</i> Fair</p> <p><i>Literature search</i> Fair</p> <p><i>Quality assessment</i> Fair</p> <p><i>Study details</i> Poor</p> <p><i>Pooling and/or synthesis</i> Fair</p>

Study Country Grade	Aims	Included studies	Methods	Outcomes	Results	Comments
Tiesberg, 2001. ² Norway III	To present a summary of the evidence on the relationship between hospital and physician volume of activities and quality of health care for a range of diagnoses.	<p><i>Participants</i> Men who have radical prostatectomy for prostate cancer.</p> <p><i>Interventions</i> In the study derived from the inpatient sample, men undergoing prostatectomy were stratified into three groups, depending on whether their operation was conducted at a high, medium or low volume hospital.</p> <p>In the insurance-based study, hospitals were categorised by volume by quartiles.</p> <p><i>Design</i> Systematic review reporting two retrospective studies – one based on a nation-wide inpatient administrative database and one on insurance claims.</p>	<p><i>Period</i> Not stated.</p> <p><i>Adjustment for confounding variables</i> Only studies which adjusted for demographic factors and/or co-morbidity were included in the review.</p>	Relative risk of death.	<p>A US nation-wide administrative database categorised hospitals as being 'High volume' (greater than 54 prostatectomies per year), 'Medium volume' (25 to 54 prostatectomies per year) and 'Low volume' (less than 25 prostatectomies per year).</p> <p>Increased odds ratios for in-hospital mortality in low (OR 1.8; 95% CI: 1.2 to 2.7) and medium (OR 1.7; 95% CI: 1.2 to 2.6) volume hospitals were noted when compared with high volume hospitals.</p> <p>The total mortality was 0.25% for all patients.</p> <p>The analysis of the insurance database saw hospitals with low (less than 39 prostatectomies per year), medium-low (39 to 74) and medium-high (75 to 140) volumes being compared with high volume hospitals (greater than 140 prostatectomies per year). All had higher relative risk (RR) of serious complications – Low: 43% (95% CI: 37% to 48%), Medium Low: 25% (95% CI: 19% to 31%), Medium High: 9% (95% CI: 3% to 15%); readmission – Low: 30% (95% CI: 21% to 39%), Medium Low: 16% (95% CI: 7% to 25%), Medium High: 8% (95% CI: 1% to 17%); mortality – Low: 51% (95% CI: 25% to 77%), Medium Low: 43% (95% CI: 17% to 69%) and Medium High: 42 (95% CI: 16% to 48%).</p> <p>Changes in hospital volume over time were not associated with changes in rates of complications, re-admissions or deaths.</p>	<p>The studies included in the review measured mortality but did not measure the effect of increased volume on functional parameters such as incontinence or impotence.</p> <p>The authors additionally reported on a study based on a insurance database.</p> <p>This was not included in this review as it had benign and malignant prostatectomies analysed together.</p> <p>The report was published with the text in Norwegian and the tables of extracted data in English.</p> <p>US data may not be readily applicable to the NHS, but this is less of a concern in relation to clinical information such as this than managerial or organisational data.</p> <p>The study appeared to be well conducted but some literature may have been missed in their search as databases were only searched for dates after the publication of CRD Report 8.³ This cancer was not addressed specifically in that report and so literature predating the report's publication would have been missed.</p> <p><i>Inclusion criteria</i> Good</p> <p><i>Literature search</i> Fair</p> <p><i>Quality assessment</i> Fair</p> <p><i>Study details</i> Good</p> <p><i>Pooling and/or synthesis</i> Fair</p>

Table 1.1b: Concentration and specialisation of services in the treatment of urological malignancies: primary studies

Study Country Grade	Aims	Study characteristics	Outcomes	Methods	Results	Comments
Bennett, 1997. ⁶ USA VI	To assess if men with prostate cancer are more likely to undergo invasive staging tests if they are treated by urologists who have higher caseloads than urologists with lower caseloads.	<p><i>Patient information</i> Men with cancer of the prostate.</p> <p><i>Hospital/professional information</i> 1 university hospital.</p> <p><i>Intervention</i> Diagnostic imaging.</p> <p><i>Study population</i> 10 urologists.</p> <p><i>Time period</i> Not stated.</p> <p><i>Adjustments for confounding variables</i> Not applicable.</p>	Appropriateness of diagnostic investigations.	<p><i>Design of study</i> Case series.</p> <p><i>Statistical methods</i> Descriptive statistics.</p> <p><i>Category cut points</i> High > 20 prostatectomies per year. Medium 10 to 19 prostatectomies per year. Low < 10 prostatectomies per year.</p>	<p><i>Patients with a low PSA level</i> High volume urologists requested bone scans for 28% of men in this category. Medium volume urologists requested them for 73% and low volume urologists for 76%. Requesting bone scans is supported only in specific cases for this patient group. High volume urologists requested CT scans for 3% of men in this category. Medium volume urologists did not request CT scans for any of their patients while low volume urologists requested scans for 28% of their patients. Requesting CT scans is not supported in this patient group.</p> <p><i>Patients with a high PSA level</i> High volume urologists requested bone scans for 78% of their patients while medium volume urologists and low volume urologists requested them for 71% and 80% of their patients respectively. This is an appropriate intervention in this patient group. No CT scans were requested by high or medium volume urologists but 40% of patients of low volume urologists had this investigation.</p>	<p>The authors failed to identify the proportion of patients in the high and low PSA categories.</p> <p>A significant weakness of the study is that the high and medium volume categories each consisted of only two urologists.</p>
Howard, 1995. ⁵ Scotland VI	To present a detailed case note review of patients registered with testicular non-seminoma germ cell tumours (NSGCT) between 1983 and 1988 under the Scottish Cancer Registration Scheme and who had died by 1992.	<p><i>Patient information</i> Patients NSGCT.</p> <p><i>Hospital/professional information</i> 5 cancer units.</p> <p><i>Intervention</i> Surgery, radiotherapy and chemotherapy.</p> <p><i>Study population</i> Patients.</p> <p><i>Time period</i> 1983 to 1988.</p> <p><i>Adjustments for confounding variables</i> None.</p>	<p><i>Survival.</i> Proportion of treatments judged to be sub-optimal.</p>	<p><i>Design of study</i> An audit of clinical records of patients identified from a national registry.</p> <p><i>Statistical methods</i> χ^2 Kaplan Meier Spearman's Rank</p> <p><i>Category cut points</i> Absolute volumes of each individual hospital.</p>	<p>All cause deaths and deaths from NSGCT were lowest in Centre E which treated most patients (192) and highest in Centre A which treated fewest patients (15). Survival varied between 70.4% in Centre A and 94.2% in Centre E ($\chi^2 = 14.46$, 2 d.f., $p < 0.006$). However, use of the Spearman's rank test yields a non-significant trend in this instance ($R_s = 0.7$, $p > 0.20$). 25 patients were judged to have had 'sub-optimal treatment'. Differences between treatment centre ($\chi^2 = 4.24$, 4 d.f. $p > 0.1$) were found but did not reach significant levels. Centre C had lower volumes but had levels of 'sub-optimal' treatment more characteristic of a larger unit. When omitting cases of lack of compliance, delay in referral or the complications of other medical conditions, there appears to be an inverse relationship between size and number of patients with sub-optimal management (A = 20%, B = 9.8%, C = 5.9%, D = 3.7% and E = 1%).</p>	<p>The authors suggest that reaching statistical significance was made less likely by the small number of centres and the small number of patients treated at some centres.</p> <p>Its location permits ready application to the NHS as a whole.</p>

Study Country Grade	Aims	Study characteristics	Outcomes	Methods	Results	Comments
Klepp, 1991. ⁷ Norway, Sweden VI	Report the findings of the SWENO-TECA project, in relation to therapeutic outcomes and implications for future management of patients with NSGCT in early clinical stages.	<p><i>Patient information</i> Patients registered with the project and treated in participating regional centres in Norway and Sweden.</p> <p><i>Hospital/professional information</i> 16 regional centres.</p> <p><i>Intervention</i> Clinical staging.</p> <p><i>Study population</i> Men with NSGCT (n = 345).</p> <p><i>Time period</i> 1981 to 1986.</p> <p><i>Adjustments for confounding variables</i> Only early stage patients were included.</p>	Accuracy of clinical staging.	<p><i>Design of study</i> Prospective cohort study.</p> <p><i>Statistical methods</i> Sensitivity, specificity and accuracy measurements.</p> <p><i>Category cut points</i> Not given.</p>	<p>Low accrual hospitals treated a mean 1.7 patients per year. Medium accrual hospitals treated a mean 6.2 patients per year and high accrual hospitals treated a mean 24.2 patients each year.</p> <p>The high accrual hospital had significantly better sensitivity ($p < 0.048$) but significantly poorer specificity ($p < 0.043$). There were no significant differences in the overall accuracy of the hospitals in the three categories.</p>	<p>A weakness of the study is that only 345 of 548 patients are included in this assessment. Additionally, it is not clear how many hospitals are in each group. From the text it seems that the high accrual figures relate to only one hospital.</p> <p>The authors do not give any information on the characteristics of the populations served by the regional units so it is difficult to assess relevance to the hub/spoke system of centres and units in the NHS.</p> <p>The authors do not state if the clinical staging was done by urologists, oncologists or a combination of these professionals.</p>



Study Country Grade	Aims	Study characteristics	Outcomes	Methods	Results	Comments
Lee, 1999. ⁹ England VI	To assess the value of central histo-pathological review of testicular tumours.	<p><i>Patient information</i> Men with testicular tumours.</p> <p><i>Hospital/professional information</i> 1 high volume hospital reviewing pathology slides. 12 lower volume hospitals sending slides for review.</p> <p><i>Intervention</i> Histo-pathological diagnosis.</p> <p><i>Study population</i> Not addressed.</p> <p><i>Time period</i> 1992 to 1997.</p> <p><i>Adjustments for confounding variables</i> None.</p>	Accuracy of diagnoses. Inappropriate treatments avoided.	<p><i>Design of study</i> Retrospective Cohort Study.</p> <p><i>Statistical methods</i> Descriptive.</p> <p><i>Category cut points</i> Categorical – Tertiary referral centre compared with referring units.</p>	<p>208 slides from a total of 220 during the study period were examined (94.5%).</p> <p>10 patients from outside the region whose original records were not available were excluded. 2 patients whose treatment preceded the study period were excluded.</p> <p>Twelve patients (6%) had a major change in their diagnosis.</p> <p>Five patients, previously diagnosed with classical or anaplastic seminoma, had their diagnosis altered to NSGCT.</p> <p>Three of these patients had planned radiotherapy cancelled. One patient had surgery for a mass which was residual after chemotherapy. One patient, with metastatic disease, required no change in management.</p> <p>One patient, previously diagnosed with contralateral atrophy, had his diagnosis altered to NSGCT and preceded to have a second orchidectomy.</p> <p>One patient, previously diagnosed with classical seminoma, had his diagnosis altered to lymphoma and proceeded to be managed with standard lymphoma chemotherapy.</p> <p>One patient, previously diagnosed with classical seminoma, had his diagnosis altered to spermatocytic seminoma and had planned radiotherapy cancelled.</p> <p>One patient, previously diagnosed with NSGCT, had his diagnosis altered to NSGCT/adenocarcinoma, had planned chemotherapy but had a laparoscopy brought forward.</p> <p>One patient, previously diagnosed with NSGCT, had his diagnosis altered to adenocarcinoma, but required no change in management.</p> <p>One patient, previously diagnosed with spermatocytic seminoma, had his diagnosis altered to Leydig Cell tumour, but required no change in management.</p> <p>One patient, previously diagnosed with adenocarcinoma arising in NSGCT, had his diagnosis altered to NSGCT, but he also required no change in management.</p> <p>Reports issued following review detailed the tumour elements more accurately in 47 cases of NSGCT.</p> <p>Vascular invasion was addressed in the 109 cases where an agreed diagnosis of NSGCT was made.</p> <p>59 patients (54%) had peripheral reports citing vascular invasion. This was correct in 47 cases (80%) and incorrect in 12 (20%).</p> <p>48 patients' reports (44%) made no mention of vascular invasion.</p> <p>Seven original reports used unclear terminology.</p>	<p>The study includes 'only occasional biopsies from Portsmouth'. It does not clarify why any from Portsmouth, itself a cancer centre, are included, why those which were from Portsmouth but were not included were excluded nor how those for inclusion in this study were chosen.</p> <p>The centre was judged to be correct and all errors were deemed to have occurred in the peripheral areas.</p> <p>One pathologist conducted all but 14 of the reviews.</p> <p>As an NHS hub/spoke service, this could readily apply to other locations in the NHS.</p>

Study Country Grade	Aims	Study characteristics	Outcomes	Methods	Results	Comments
Steinberg, 1997. ¹⁰ USA VI	To analyse grading patterns and accuracy in non-academic sites for correlation of prostate needle biopsy (FNB) and radical prostatectomy Gleason grade.	<p><i>Patient information</i> Men undergoing a fine needle biopsy and subsequent radical prostatectomy for cancer of the prostate.</p> <p><i>Hospital/professional information</i> 1 university hospital. Unspecified number of referring community hospitals.</p> <p><i>Intervention</i> FNB in a high volume setting.</p> <p><i>Study population</i> All men for whom histology reports from the referring hospital were available.</p> <p><i>Time period</i> 1994.</p> <p><i>Adjustments for confounding variables</i> None.</p>	Correct grading achieved with the biopsy.	<p><i>Design of study</i> Case series.</p> <p><i>Statistical methods</i> Descriptive. Correlation testing.</p> <p><i>Category cut points</i> Not applicable. (The academic centre was defined as the high volume unit whilst the referring hospitals were categorised as low volume.)</p>	<p>390 patients had biopsies in both community and academic hospitals.</p> <p>There was complete correlation between the community and academic hospitals' assigned grade for the tumour in 62% of cases (240 of 390).</p> <p>The major difference between the results of the community and academic pathological grading was that in the community setting 22% (87 patients) were assigned a Gleason grade of 2 to 4 while in the academic setting, only 1% (4 samples) were assigned gradings in this range. None of these patients were found to have grade 2 to 4 disease at prostatectomy.</p> <p>499 patients had biopsies in the academic hospital and preceded to have radical prostatectomy there.</p> <p>Of these, 82 (16%) were graded by a specialist GU Pathologist and 417 (84%) were graded by a non-GU pathologist. Agreement with the grade assigned following prostatectomy was 0.552 for the GU Pathologist and 0.545 for the other pathologists.</p>	In addition to this analysis, the paper compared the grade assigned to the tumour after each biopsy with the grade assigned after the prostatectomy. These data have not been extracted as they do not fall within the inclusion criteria.



Study Country Grade	Aims	Study characteristics	Outcomes	Methods	Results	Comments
Stockton, 2000. ⁸ England VI	An investigation into which hospitals would benefit from investment and development and which should have services restricted, with respect to the implementation of the Calman-Hine framework.	<p><i>Patient information</i> Patients registered with a number of malignant diseases (including bladder cancer) in East Anglia.</p> <p><i>Hospital/professional information</i> 3 Cancer centres and 6 district general hospitals.</p> <p><i>Intervention</i> Centre of treatment.</p> <p><i>Study population</i> All patients with a malignant diagnosis registered with the East Anglia cancer registry.</p> <p><i>Time period</i> 1989 to 1993.</p> <p><i>Adjustments for confounding variables</i> Stratified according to age. Adjusted for stage.</p>	Hazard ratios.	<p><i>Design of study</i> Retrospective analysis of registry data.</p> <p><i>Statistical methods</i> Cox's proportional hazards model.</p> <p><i>Category cut points</i> Not applicable. (The presence of a radiotherapy department was used as a proxy for high volume.)</p>	<p>Hazard ratio comparing survival to 5 years after diagnosis with bladder cancer in Group 2 hospitals (Low volume hospitals without Radiotherapy and Oncology departments) relative to Group 1 (High volume hospitals with Radiotherapy and Oncology departments) were 1.09 (95% CI: 0.96 to 1.24), adjusted for age, sex and TNM stage.</p> <p>Varying volumes within the hospital group had no effect on the hazard ratio.</p> <p>Findings for bladder cancer were age independent.</p>	The authors report that in one hospital, patients with bladder cancer were systematically under-staged leading to inappropriate treatments and poorer than expected stage specific survival data. They postulate that this will have no overall effect on pooled data but do not state if this hospital was in Group 1 or Group 2.

Table 1.2a: Multidisciplinary team membership in the treatment of urological malignancies: systematic reviews

Study Country Grade	Aims	Included studies	Methods	Outcomes	Results	Comments
Grilli, 1998. ⁴ Italy III	To assess the impact of specialisation on processes and outcomes of care for cancer patients.	<p><i>Participants</i> Patients with testicular cancer.</p> <p><i>Interventions</i> Consultation with one or more specialists or with a generalist.</p> <p><i>Design</i> Systematic review reporting on a registry-based study of Irish men with testicular cancer.</p>	<p><i>Period</i> 1980 to 1998.</p> <p><i>Adjustment for confounding variables</i> Pooling was only conducted if the adjustment for confounding variables was adequately performed.</p>	<p><i>Testicular cancer</i> Mortality.</p>	<p><i>Testicular cancer</i> Consultation with a urologist was associated with improved survival and appeared more important than consultation with an oncologist in Ireland.</p>	<p>The differences between the NHS and the Irish healthcare system as well as the age of the study, may adversely affect the transferability of the results to the UK setting.</p> <p>The review is comprehensive and well conducted.</p> <p>There is only a small section dealing with urological cancers and details of the individual studies are not comprehensive.</p> <p>Data were presented in graphical format with little accompanying text.</p> <p><i>Inclusion criteria</i> Good</p> <p><i>Literature search</i> Fair</p> <p><i>Quality assessment</i> Fair</p> <p><i>Study details</i> Fair</p> <p><i>Pooling and/or synthesis</i> Fair</p>



Table 1.2b: Multidisciplinary team membership in the treatment of urological malignancies: primary studies

Study Country Grade	Aims	Study characteristics	Outcomes	Methods	Results	Comments
Valicenti, 2000. ¹¹ USA VI	To report on a university hospital's experience with a Multidisciplinary Uro-Genital Oncology Clinic (MDUGOC).	<p><i>Patient information</i> Men with prostate cancer.</p> <p><i>Hospital/professional information</i> One university hospital.</p> <p><i>Intervention</i> Attendance at a multidisciplinary urological oncology clinic.</p> <p><i>Study population</i> Attendees at the clinic for one year.</p> <p><i>Time period</i> Not stated.</p> <p><i>Adjustments for confounding variables</i> None.</p>	<p>Reason for attendance at the clinic.</p> <p>Discipline of the physicians consulted.</p> <p>Satisfaction with information.</p> <p>Patients ability to make decision on treatment preference.</p>	<p><i>Design of study</i> Postal questionnaire.</p> <p><i>Statistical methods</i> Descriptive statistics.</p> <p><i>Category cut points</i> Not applicable.</p>	<p>Questionnaires were returned by 221 of 275 men who attended the clinic within a one year period (response rate = 80%).</p> <p>All of the patients were seen by a urologist. In addition, 41% of patients consulted a radiation oncologist. 5% of patients consulted a medical oncologist.</p> <p>60% of patients attended the clinic for a second opinion. 91% of patients were very satisfied with the adequacy of the information. 96% of patients were able to decide on the best course of treatment for them after their consultation. 67% of patients had decided to have their treatment at the facility which operates the MDUGOC.</p>	<p>The report describes the patients' experiences with the clinic but is not comprehensive in reporting the results – for example 60% of patients attended for a second opinion but no reasons are given for the remaining 40%.</p> <p>No consideration is made of the possibility that the 20% of patients who did not respond may have been more likely to be unsatisfied.</p>

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Diagnosis and Assessment

The Questions

- a) What is the efficacy and diagnostic yield of performing digital rectal examination (DRE) in primary care?
- b) Do rapid access clinics, dedicated to the investigation of patients with haematuria, affect the outcomes of patients with urological malignancies?
- c) What is the efficacy of CT scanning compared with MRI in the staging of prostate, bladder, testes and renal cancers and the diagnosis of metastases?
- d) What is the efficacy of plain film chest radiography (CXR) in the diagnosis of lung metastasis in men with testicular cancer?
- e) What is the optimum frequency of CXR in the diagnosis of lung metastasis in men with testicular cancer?
- f) What is the efficacy of bone scans in the detection of bone metastasis in the diagnosis of urological cancers?
- g) How often should cystoscopies be performed in the follow-up of bladder cancer?

The Nature of the Research Evidence

a) Digital rectal examination

One well conducted systematic review was located.¹ The authors of the review conducted a meta-analysis of 14 primary studies assessing the role of DRE in primary care. No additional studies were located in supplementary searching (Table 2.1).

b) Rapid access clinics

Five studies were identified which described rapid access haematuria clinics.²⁻⁶ One of these reported a method which could assist decision making and be used by GPs to estimate the probability of serious pathology for patients presenting with haematuria.⁶

A registry-based study assessed the influence of the process of care on survival in bladder cancer patients.⁷

c) CT versus MRI

Thirteen studies were located which directly compared CT with MRI in patients with urological malignancies⁸⁻²⁰ (Table 2.2). Two studies investigated CT and MRI in the staging of cancer of the prostate.^{13, 17} Four of the reports investigated the staging of bladder cancer.^{9, 12, 16, 19} Seven studies investigated the staging of

renal cell carcinoma.^{8, 10, 11, 14, 15, 18, 20} No evidence was found in relation to testicular or penile cancer.

d) Chest radiography

Seven studies were located which addressed the area of imaging of the chest in men with cancers of the testes²¹⁻²⁷ (Table 2.3). Two of the reports pertain to patients with seminoma^{21, 25} and two to patients with NSGCT.^{22, 26} The remaining three reports pertain to a mixed group of patients.^{23, 24, 27} All seven studies included patients in remission. Two studies additionally included new patients being staged.

All seven studies were of a retrospective nature and were of comparable quality. In each case, data were collected from the patients' notes. All studied clearly defined samples and provided clearly stated criteria for inclusion and exclusion. The length of follow-up was appropriate for the disease in all instances. Additionally the outcomes measure – incidence of intrathoracic metastases and time to recurrence as well as diagnostic indicators for the tests used – were appropriate for the patient population.

e) Frequency of chest radiography

No study assessed the effects of the timing of follow-up visits or the interval between visits but five studies gave information pertinent to the subject²²⁻²⁶ (Table 2.3).

f) Bone scans

Twenty-one case series were located²⁸⁻⁴⁸ (Table 2.4). Of these the majority studied men with prostate cancer. One study dealt with cancer of the bladder, one study with renal cancer and one study with testicular cancer. One series, in the area of prostate cancer, was conducted prospectively;²⁸ the remaining series were retrospective studies.

Prostate cancer

Although 18 studies were located, none directly assessed the diagnostic accuracy of bone scanning in the identification of bone metastases in men with prostate cancer in comparison with another gold standard investigation. This was because bone scanning is regarded by many as the gold standard investigation in this population. Pathological confirmation of metastatic bone disease is rarely obtained.

The studies which were reviewed aimed to identify those sub-populations of prostate cancer patients who would not benefit from a bone scan.²⁸⁻⁴⁵ They were of a broadly similar design. The bone scan was used as the standard investigation and the other parameters being investigated were compared with the bone scan result. In the majority, individual patients were used as the unit of analysis – each patient being included only once. In two studies the consultation was the unit of analysis. In these studies patients who attended the investigators' clinic more than once and had more than one bone scan during the study period contributed more than one set of data to the analysis.^{39, 40} In each case, data collection was based on an analysis of clinical records. One study pertained to men with proven metastatic disease.³⁹

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While all of these studies had similar aims, not all assessed the same biochemical or clinical indicators. None addressed only one test. Being investigated in 16 studies, the most commonly studied test was the serum level of the Prostate Specific Antigen (PSA).^{28, 29, 31-38, 40-45} Six related to the tumour grade.^{31, 33, 35, 42, 43, 45} Five studies examined the clinical tumour stage.^{31, 35, 42, 43, 45} Bone pain was examined in five reports.^{30, 32, 34, 36, 42} Five reports examined a variety of other biochemical markers.^{28, 30, 33, 34, 39}

Of the series which reported on prostate cancer, 14 relate exclusively to men who were newly diagnosed with cancer.^{29-36, 38, 41-45} Two reports include both men with newly diagnosed prostate cancer and men with previously treated prostate cancer.^{28, 37} One of these separated patients into one of three groups depending on the type of treatments the patients had received.³⁷ The other study enrolled men with biochemical evidence of recurrence.⁴⁰

Testicular cancer

One case series from Brazil assessed bone scanning in comparison with more conventional radiographic techniques for patients with testicular cancer.⁴⁶ The reported series however gave very little information on the efficacy of the modality in this patient group.

Bladder cancer

One report from Norway assessed if the addition of an alkaline phosphatase test would improve the accuracy of a bone scan in patients with cancer of the bladder.⁴⁷ Again, this study was retrospective in nature.

Renal cancer

One report assessed a group of 36 patients in Austria with renal cell carcinoma who had a high pre-test probability of bone metastases based on other clinical information.⁴⁸

g) Frequency of cystoscopies

No study was found that specifically addressed the question of how many cystoscopies should be performed in bladder cancer follow-up. One US cost-effectiveness study, published as an abstract only, used a Markov decision analytic model to compare outcomes in patients with superficial transitional cell cancer of the bladder, followed up with frequent cystoscopies as per standard practice to a strategy of less frequent cystoscopies.⁴⁹ One RCT was found that looked at prolonging follow-up in patients with superficial bladder tumours.⁵⁰ However, most of the follow-up visits included an examination of the bladder using trans-abdominal ultrasound, with cystoscopy being performed in all patients only once a year.

Five uncontrolled studies looked at how long follow-up with cystoscopy should be continued in patients with bladder cancer.⁵¹⁻⁵⁵ Two studies, one based in Turkey and one based in Sweden included participants with non-invasive grade 1 to 2 bladder carcinomas.

Summary of the Research Evidence

a) Digital rectal examination

In a meta-analysis of DRE in primary care, the pooled estimates of specificity (0.94; 95% CI: 0.91 to 0.96) and negative predictive value (NPV) (0.99; 95% CI: 0.98 to 0.99) were high. The estimates of sensitivity (0.59; 95% CI: 0.51 to 0.67) and positive predictive value (PPV) (0.28; 95% CI: 0.20 to 0.36) were low however. When strict methodological criteria were applied to the data, nine of the 14 studies were excluded, but this had only a marginal effect and very similar overall results were found. These results imply that DRE is an appropriate initial intervention in the management of prostatic symptoms and a negative result will have a high predictive value. A positive result of DRE is not sufficient evidence for a GP to make a firm diagnosis of prostatic disease however, but rather indicates the need for further investigation and/or referral.¹

Conclusions

DRE is an appropriate intervention in the general practice setting. A negative DRE conducted by a general practitioner will be highly predictive of the absence of cancer. However, a positive DRE conducted by a general practitioner will not be strongly predictive of cancer but will instead indicate the need for further investigation and/or referral.

b) Rapid access clinics

In all the five studies reviewed, which described a newly established haematuria clinic, the authors reported the rate of serious pathological findings.²⁻⁶ One study additionally compared the presenting signs and symptoms of haematuria and made efforts to define their predictive values.⁶ However, none of the researchers assess outcomes such as mortality or survival. Each study was predicated on the assumption that more expedient diagnosis would improve outcomes such as survival² or morbidity⁴ or facilitate appropriate investigation⁵ but no evidence is presented to support these premises.

Registry data from the South East and South West Thames health regions however appears to contradict these assumptions.⁷ Reviewing data on 609 patients with bladder cancer, little evidence was found that variables relating to the process of care contributed to the overall survival of the patients.

Conclusions

Evidence from the review has failed to support the belief that rapid access to haematuria clinics improves outcomes for patients. The evidence in relation to rapid access clinics in urological oncology related exclusively to clinics which were established to examine patients with haematuria. Studies were predicated on the assumption that early diagnosis improved outcomes. While early diagnosis may lead to increased likelihood of cure, no evidence was given to support or oppose this premise. On reviewing the evidence located, no firm conclusion about the possible benefits of these clinics may be made.

c) CT versus MRI

Prostate cancer

Two studies investigated the accuracy of the CT and MRI in assessing seminal vesicle invasion and lymph node involvement.^{13, 17} Both studies showed a 7.5% increased accuracy of MRI over CT for the detection of invasion of the seminal vesicles and a 11.9% to 13.4% increased accuracy of MRI over CT in the detection of lymph node involvement. One of the studies also demonstrated a 25.9% increase in the accuracy of MRI over CT in the detection of extra-capsular extension.¹⁷

Taken together, these imply that MRI is the optimal imaging modality but both studies suffer from important methodological flaws. The German research involved a total of 103 patients but only 63 men had CT and 52 men had MRI.¹³ The different populations investigated with each modality may have an effect on the validity of the research. The Japanese study investigated a total of only 18 patients and chance effects cannot be precluded.¹⁷ In addition, both these sources are relatively old. As such no firm conclusions may be drawn from the review.

Bladder cancer

No clear pattern emerged in the studies which were located.^{9, 12, 16, 19} One study of 22 patients from Germany showed MRI as being more accurate than CT but with 25% of patients having their disease overstaged; CT was unlikely to overstage but 22% of patient had their disease understaged.¹² A Japanese series of 28 patients showed a marginal gain for MRI over CT but this was based on the results of only two patients.¹⁹ An Italian study, however, involving 23 patients found the two techniques comparable.¹⁶ A US study of 36 patients compared CT with an MRI protocol involving T1, T2, dynamic gadolinium enhanced spoiled GRE and late gadolinium enhanced T1 techniques. It found that the combined protocol was accurate for 75% in staging patients compared with 55% for CT. However, CT had performed marginally better in diagnosing the malignancy.⁹

Renal cancer

In the reports pertaining to the planar imaging of renal cell cancers (RCCs), a slight advantage was seen in MRI over CT in three studies which gave information on the overall stage only.^{8, 11, 15} Contrast enhanced MRI was found to be preferable to non-contrasted MRI in one of these studies.¹⁵ Four studies giving information on the component factors of staging in RCC all found the techniques to be comparable.^{10, 14, 18, 20} Regarding the staging of extension into the local venous structures, one report found MRI with T1 and FLASH sequencing to be more accurate than CT (MRI – 91.3% to 95.7% compared with CT – 81.4% to 88.4%).¹⁸

The same four studies assessed the modalities' abilities to diagnose lymphatic involvement. Two of these studies found comparable results from the modalities.^{14, 18} The other two studies found MRI to be 9.8%¹⁰ and 12.0%²⁰ more accurate than CT in identifying metastatic deposits in lymph nodes.

It should be borne in mind that these studies included a small number of patients (mean n = 46, range 24 to 79). This may affect the results. Additionally, all but one of these studies are from the first half of the 1990's. Both MRI and CT technology and practice has developed in the time since these studies were conducted. This could have affected the results considerably. One report cited the ability of MRI to provide sagittal images as being key to its advantages over CT.⁸ This facility was unavailable with serial CT scanners, state of the art in the early 1990's; modern spiral CT scanners have this option however.

Conclusions

The evidence reviewed showed MRI as having a clear advantage over CT in the staging of men with prostate cancer. This was particularly true in the assessment of local invasion. However, one study reviewed had methodological flaws and the other evaluated only a small number of patients.

Evidence on the choice of imaging modality for the assessment of patients with bladder cancer was inconsistent. Neither modality was proven to be superior to the other. Additional research is required to resolve this question.

In patients with renal cancers, MRI proved to be marginally better than CT. This was true in identifying the overall stage of the disease and also in identifying the extent of lymphatic involvement. It is important to remember that the number of patients studied in most of these studies were not large and that the majority of studies in this area are from the early nineties. The development of imaging technology and practice since that time may influence the applicability of this conclusion to current practice.

d) Chest radiography

Evidence suggests that the use of both computed tomography of the chest (CTC) and plain film chest radiography (CXR) is unjustified.²¹⁻²⁷ While there is debate as to which modality is superior, it appears from the limited evidence that CTC is more accurate. However, the magnitude of the advantage was not large and is based on a small number of retrospective studies of varying quality and not all of the studies came to the same conclusions. In the seven series analysed the number of patients ranged from 58 to 503.

The best evidence comes from studies which compare the results of a group of patients who underwent both investigations as well as a gold standard investigation. While the ideal gold standard investigation would involve histological confirmation of the presence and extent of the malignancy, this is not feasible or ethical in the case of lung metastases.

In studies such as these, blinding of the professional reporting the test is seen as a sign of high quality research. In the seven series studied, the original radiological report was used in all but one case. In the remaining case, the original reports were compared with other clinical details.²⁷ Blinding of the original reporting radiologist was not addressed in any of the studies but normal practice involves providing the radiologist with as much clinical information as possible to assist the interpretation of the image. The use of this quality criterion would not appear justified in these series. However, as the radiologists

were not blinded, it is difficult to ascertain the unique relative contributions of the images and the other clinical details to the overall report.

Only two studies reported sufficient data to compare the diagnostic tests with a standard test.^{25, 27} In both studies the gold standard diagnosis of metastases was made when imaging, biochemistry and clinical symptoms of the patient had been taken into account. The overall accuracy of CTC was higher than CXR in both series.

One of these studies found that CTC was more sensitive than CXR although the specificity of the modalities were comparable.²⁵ This series stratified the patients according to the results of their abdominal CT scans. The sensitivity of both investigations was equivalent in those men with no metastatic abdomino-pelvic metastases. CXR showed a marginally increased specificity in this group. In men with abdominal disease however, CTC proved to be more sensitive than CXR (100% as against 77.8%) and only marginally less specific. About one fifth of patients in this group with a negative CXR actually had metastatic chest disease.

In the other study, the agreement of the CTC with the gold standard diagnosis was higher than that for CXR (98.7% as opposed to 90.1%).²⁷ The kappa statistic for agreement with the standard diagnosis was higher for CTC ($\kappa = 0.96$; 95% CI: 0.95 to 0.97) than for CXR ($\kappa = 0.65$; 95% CI: 0.62 to 0.68).

The remaining studies report the patterns of recurrence in the patient population studied. In these series, not all patients had both CTC and CXR, but rather, the patient's clinicians decided which modality to use. These data are much more open to bias.

In a series of 334 patients, 29 of whom recurred, two recurrences were identified by routine CTC's. Tumour markers demonstrated that 20 patients had recurrent disease. The remaining patients were identified by CT (five cases) or CXR (two cases) which were conducted following the reporting of suspicious symptoms.²³

In a review of 58 patients from a US military hospital, two of 58 patients recurred and neither was identified by routine investigations but both were imaged following reports of symptoms by the patients involved.²¹

A review of 154 patients with NSGCT found that of 29 patients who suffered a thoracic recurrence only two were visible on CXR and that these had been identified by other means prior to the CXR.²² Computerised tomography was used to identify 33 of 42 patients who had recurred. However, data were not presented on the proportion of patients with thoracic recurrence identified by chest CT scanning however.

Two additional studies were located in which CXR was a standard part of the follow-up schedule but CTC was not. A German series of 503 patients found that ten of 16 men with thoracic metastases were identified by CXR while two were identified by CTC. CTC was however not a routine investigation in this series.²⁴

A Canadian series of 170 men found that all patients with thoracic metastases were identified by tumour markers, CTC or examination with history and that CXR added nothing to the diagnostic programme.²⁶

However, in addition to the accuracy of the investigations, other factors will influence the choice of test used. One series calculated for instance that the radiation dose absorbed during CTC was on average 84 times that of CXR.

Conclusions

It appears from limited evidence that CTC is superior to CXR in detecting metastatic deposits in the thorax in men with testicular tumours. In particular, men who have metastatic abdominal deposits were found in this review to benefit from CTC. The magnitude of the advantage was not large and this conclusion is based on a small number of studies of varying quality.

e) Frequency of chest radiography

No direct evidence was found which addressed the question of the optimum timing and frequency of follow-up clinic visits. However, a number of studies give insight into the issues involved. A number of the cases series gave information on the patterns of recurrence which may be used to inform the question of follow-ups in this patient group.²²⁻²⁶

The number of recurrences in the series ranged from ten to 48 patients. In one study, 28% of recurrences occurred within the first year (n = 42).²³ In the others, the proportion of recurrences within one year was 70% (n = 10),²⁵ 79% (n = 48),²⁶ 81% (n = 33)²⁴ and 90% (n = 42).²²

Data for the proportion of recurrences within two years were 40% (n = 42),²³ 80% (n = 10),²⁵ 84% (n = 33),²⁴ 100% (n = 48)²⁶ and 100% (n = 42).²²

No patient recurred more than three years after diagnosis in two series.^{22, 26}

Data for the proportion of recurrences more than three years for the remaining series were 7% (n = 42),²³ 9% (n = 33)²⁴ and 20% (n = 10).²⁵

Conclusions

No direct evidence was found and as such no conclusion may be drawn. However, information on the natural history of the disease was located and this may inform the choice of a follow-up schedule and the role of imaging within it. Most studies reviewed saw the majority of recurrences within the first year while recurrence after the second year was uncommon.

f) Bone scans

Prostate Cancer

Prostate Specific Antigen (PSA) testing Data from five of the series show that the mean PSA of men with metastatic cancer is higher than those men who do not have metastases.^{32, 33, 40, 41, 43} Three series showed that the PSA rose as the burden of metastatic disease rose.^{32, 43, 44} However, considerable overlap was noted in the PSA levels of metastatic and non-metastatic patients in these series and as such there is insufficient evidence to support the replacement of bone scans with PSA testing in assessing the extent of metastatic spread.

PSA levels vary across a wide range and there is no agreed PSA level below which is considered normal or above which is considered abnormal. Setting a value which will act as a cut point is a matter of clinical judgement. Choosing a

low value will pick up all cases (i.e. be sensitive) but may include many men who do not have metastatic disease. However, choosing a high level as the cut off will mean that only men with the disease will be identified (i.e. be specific) and as such men without the disease will not need to be tested further. On the other hand, with a specific test, some men who have metastatic disease may be inadvertently missed.

Two case series used Receiver Operator Characteristics (ROC) curves to find the cut point affording the best compromise between high sensitivity and high specificity.^{33, 35} One series from Italy found that a cut point of 35ng/ml provided optimal results³³ while a Spanish series gave a figure of 70ng/ml.³⁵

Variation existed in the sensitivity and specificity of the PSA test between the 16 series reviewed. It is important to consider that the sensitivity and specificity of a test are related variables and are dependent on the population to which the test is applied. Insufficient details were presented in the studies to choose a fixed sensitivity value and carry out a direct comparison of the resultant specificity values (or to choose a fixed specificity value and carry out a direct comparison of the resultant sensitivity values).

Instead the studies reported values relative to specified cut points. Taking the example of using a 10ng/ml cut point, sensitivity varied between 53.3% (with a corresponding specificity of 76.3% in a series of both new and previously treated men)²⁸ to 100% (with corresponding specificities of 30%,³⁸ 33%³² and 36%³³ in three series of newly diagnosed men only). Specificity varied between 21.5% (with a corresponding sensitivity of 92.5%)³⁵ and 76.3% (with a corresponding sensitivity of 53.3%).²⁸ The NPV ranged from 91.5%³⁵ to 100%^{30-32, 38, 44} in newly diagnosed men and was at 87.1% in a series combining newly diagnosed previously treated men.⁴¹ As such, a man is unlikely to be found to have metastatic disease with a PSA level below 10ng/ml.

The patient populations varied considerably across the series however. It is possible that these differences in patient characteristics may have affected the results obtained. Variation in the percentage of patients who had metastatic disease at diagnosis are a good example of this; rates varied from as low as 6%²⁹ to as high as 40%.³⁸ Similar variations were seen in the rates of patients presenting with late stage disease and higher grades of tumours. It is also impossible to explore fully the influence of differences in the populations studied on the results obtained in the various series.

The research also varied in terms of quality. The retrospective nature of the majority of these case series means they are open to biases and to problems of missing information. All but one were retrospective. Some of the included studies recruited a small number of patients. Not all of the studies gave details on the processes used in conducting the research while others gave fuller details of their methods.

Nevertheless, the studies reported broadly similar results despite variations in the standard of reporting.

Two series included men who had been treated with androgen ablation – the suppression of the male hormones.^{37, 40} Ablation may be achieved by orchidectomy or by chemical castration. Androgen ablation is believed to reduce the PSA levels of patients which was substantiated in the current series.

One of the series compared three groups of patients;³⁷ newly diagnosed men (n = 10), men who had non-androgen ablative therapy (n = 29) and those who had undergone androgen ablation (n = 9). The men who had had ablation therapy had a mean PSA level of 16.6ng/ml compared with 34.5ng/ml for men who had undergone other forms of therapy and 180.3ng/ml for newly diagnosed men. Four of the nine patients in the androgen ablation group had PSA levels within normal limits (i.e. below 4ng/ml). However, two of these men had metastatic disease.

Mean PSA levels were also found to be lower in hormonally treated men (3ng/ml) than in men who had received only surgery and/or radiotherapy (383ng/ml) in a similar series.⁴⁰

Histological grade While the use of four different staging systems make comparison difficult, men with less well differentiated disease were more likely to have metastatic disease.^{31, 32, 35, 42, 43, 45}

An example of this can be seen in a review of 631 patients where men with poorly differentiated cancer were found to be 2.25 times more likely (95% CI: 1.43 to 3.54) to have metastatic disease than men with well differentiated disease.⁴⁵ However, an Italian series found that the predictive value of tumour grade was less than the influence of PSA and PAP levels. The area under the ROC curve was 0.61 for tumour grade but 0.93 for PSA and 0.81 for PAP levels.³³

Clinical stage While comparisons are not facilitated by the use of multiple staging systems, those patients with more locally advanced disease were more likely to have metastatic deposits. A series of 189 patients from Spain found a greater proportion of men with T3 or higher had metastatic disease than those with less advanced disease.³⁵ A US series found a greater proportion of men with Stage T2c disease or higher had a greater probability of metastatic deposits.⁴⁵

Bone pain Of patients with metastatic bone disease, 52.2% had pain while only 11.8% of patients with no metastatic bone disease were found to have pain in a series of 40 patients from Turkey.³⁴ In a series of 129 patients from Argentina, 96.6% patients with bone pain had metastatic disease compared with only 29.3% of those without bone pain.³⁶ In a US series of 852 patients, seven patients had metastatic disease at diagnosis and five of these reported pain.⁴² The site at which the patient reported the pain did not always correlate well with the location of metastatic deposits identified on bone scans.³²

Two series investigated the combination of biochemical analysis and the patients' reports of pain. An Argentinian series of 129 patients studied the combination of PSA and bone symptoms. All 29 patients who had normal PSA and who were free of bone pain were free of metastatic deposits on their bone scans. All patients with a PSA above 20ng/ml and who had bone pain had metastatic disease demonstrated on bone scanning.³⁶ A US review of 288 patients who were classified as 'at risk' of bone metastases if they had abnormal acid phosphatase, alkaline phosphatase or bone pain found that only 1.4% of men who had none of these indicators had metastases.³⁰

Biochemical markers Prostatic acid phosphatase (PAP) was investigated in a series of 118 patients from Italy but was found to be less useful than PSA testing.³³ Serum alkaline phosphatase (SAP), total acid phosphatase (TAP) and

PAP were evaluated in a Turkish series of 40 patients along with PSA testing. The PSA test was found to be the most accurate.³⁴ A Japanese study investigated osteoblastic and osteoclastic markers as well as PSA. Deoxypyridinoline, alkaline phosphatase, bone related alkaline phosphatase and pyridinoline cross-linked carboxyterminal telopeptide (1 CTP) were studied and found to be related to the probability of metastatic disease, but only the latter marker was significantly so. Additionally osteocalcin was studied and no correlation with the extent of disease was found.²⁸ A Turkish series of 21 patients found the SAP had an accuracy of 86.9% in predicting bone scans.³⁹

Clinical performance status The predictive value of the Karnofsky Scale of clinical performance was evaluated in one series. This measure was accurate at identifying patients with metastatic bone disease in 85.7% of cases.³⁹

Testicular cancer

A total of twenty-five percent of patients with testicular tumours had bone metastases identified on their bone scans.⁴⁶ As with much research in the area of testicular tumours however, the number of patients in this series was small; forty patients were included in the study. While little information was given on the process of conducting the research, a major failing was that bone scanning was compared with plain film radiography only; cross sectional imaging was not assessed. Additionally, the study reports information on the patterns of radioactive uptake but fails to compare areas of increased uptake with any gold standard. As such no conclusions as to the efficacy of the modality should be drawn from this study.

Bladder cancer

Bone scanning as used in a series of 227 patients was unable to identify patients for whom radical cystectomy was an appropriate intervention. No conclusions are able to be drawn about the effectiveness of adding SAP to bone scanning from these results.⁴⁷

Renal cancer

One study investigated patients who had a perceived high pre-test probability of bone metastases based on other clinical information such as abnormal biochemistry, bone pain or pre-existing soft tissue metastases.⁴⁸ Fourteen patients had metastatic disease identified by computed tomography or bone biopsies. Only one of these patients had a positive bone scan giving a sensitivity of only 7% for this modality. This finding does not support the use of bone scanning in the examination of patients with renal cell carcinoma even if they have a higher likelihood to have bone metastases in comparison with other patients with renal tumours. The small number of patients studied means that the research should not be regarded as conclusive.

Conclusions

The use of bone scans is well established in the detection of bone metastases in prostate cancer. However, the process is time consuming and expensive. It involves the use of radioactive markers and is open to questions regarding its specificity. As such, much research is aimed at identifying groups of patients in whom bone scanning may be safely omitted.

Biochemical testing of serum samples was the commonest diagnostic strategy identified. Clinical signs and symptoms have also been researched. In the detection of bone metastases from cancer of the prostate, however, it appears that PSA testing offers the best means of identifying men at increased likelihood of having bone metastases. Research suggests that men with serum PSA below 10ng/ml are unlikely to have prostate cancer metastatic to their bones.

Androgen ablation therapies suppress the PSA level during the treatment but also have a suppressive effect after the therapy has stopped. A low serum PSA level in a man who has received androgen ablation is not sufficient to preclude the possibility of metastatic bone disease.

Other biochemical markers including total and prostate acid phosphatase, alkaline phosphatase and a range of other osteoclastic and osteoblastic markers were evaluated in the studies which have been reviewed. While some markers were more useful than others, none proved superior to serum PSA testing. Some markers may prove to be beneficial when used in addition to the PSA test but additional research is required to identify the most useful combinations of tests.

In the other urological malignancies, research is much more limited. One study found bone scanning to be of limited value in patients with bladder cancer and another found no evidence to support the use of bone scans in patients with kidney cancer, even if they were at greater risk of have metastatic bone disease. A methodologically weak study failed to find any advantages of bone scanning over conventional imaging.

However, the lack of corroborating studies in the areas of bladder, testicular and renal cancer means that no firm conclusions should be drawn from this review. Additional research is needed before an assessment of the evidence base of bone scanning in these populations is possible.

g) Frequency of cystoscopies

One US cost-effectiveness study compared the use of frequent cystoscopies, as per standard practice, with less frequent cystoscopies.⁴⁹ Standard practice included cystoscopy every three months for the first two years, every six months for the next year, annually thereafter and starting again at every three months for tumour recurrence. Infrequent follow-up included cystoscopy every six months for the first year, every nine months for the next year, annually thereafter and starting again at every six months for tumour recurrence.

For standard practice, rates of tumour recurrence, tumour progression to Stage T2 or greater and rates of death from bladder cancer were determined from the literature. Rates for infrequent cystoscopies were determined from review of charts and tumour registry abstracts of a cohort of 193 patients diagnosed with superficial bladder cancer (Stage Ta grades 1 to 2) between 1950 to 1965 and followed long term. The results with regard to rate of recurrence, progression and death were not reported. Compared with infrequent cystoscopies, standard practice resulted in approximately one additional day of life per cystoscopy. The authors concluded that frequent follow-up of cystoscopy did not yield a clinically meaningful increase in life expectancy and the cost of this strategy may be unacceptably high.

2

One Danish trial evaluated the consequence of doubling follow-up intervals for patients with non-invasive bladder tumours (Stage Ta, grade 1 and 2) (n = 102; 97 of whom were evaluable).⁵⁰ Patients were randomised to one of two follow-up regimens: every three months for the first two years and every six months in the third year, thereafter once a year (group 1, n = 45); or every six months for the first year and once a year thereafter (group 2, n = 52). However, follow-up visits usually entailed the use of trans-abdominal ultrasound with cystoscopy only performed once a year in all patients.

The trial found no difference between the two groups in terms of recurrence, progression or tumour-related deaths. The median follow-up in Group 1 was 30.6 months (range 22.8 to 39.1) and the median follow-up in Group 2 was 26.6 months (range 14.7 to 34.1). The total number of follow-up visits in the second regimen was reduced by 37.5% (p = 0.0016) compared with the first regimen. The number of follow-up visits at which patients present with a recurrence was increased by 65% (p = 0.0475).

Additionally, a number of case series were located.⁵¹⁻⁵⁵ Valid comparisons of the results of different case series are difficult to make as the potential for bias is quite high. This is owing to differences in case mix, co-morbidity, treatment regimes followed and the skills and preferences of the medical personnel involved.

Conclusions

Direct evidence to answer this question was not located. A firm conclusion cannot be formulated. However, indirect evidence was found. A cost-effectiveness study found no clinically meaningful advantage in frequent cystoscopies over less frequent follow-up and found significant financial savings could be made if the frequency of follow-up was reduced. An RCT where frequent follow-up was compared with infrequent follow-up in patients with superficial bladder cancer found no difference in the clinical performance of the two groups. Cystoscopy was not the predominant assessment modality however. Taken together these studies suggest that it may be possible to reduce the frequency of cystoscopy, but further research is needed to clarify this finding and to discover its applicability to the situation in the NHS.

Table 2.1: Digital rectal examination (DRE) in primary care: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comment
Hoogendam, 1999. ¹ I	A systematic review of the available data to determine the diagnostic value of DRE for prostate cancer in a primary care setting.	All patients underwent testing with PSA, TRUS or both. All patients with a positive DRE and in cases with a negative DRE those with a positive score in another test. Reference test performed on more than 90% of the people eligible for the test.	Sensitivity. Specificity. Positive predictive value (PPV). Negative predictive value (NPV).	14 RCTs, comprising 21,839 patients. Prevalence rates of detected cancers ranged from 1.2 to 7.3%. Calculated Spearman's rank coefficient of Sensitivity and 1 – Specificity was statistically non-significant (p = 0.12). Pooling of the results of all 14 studies revealed:- Sensitivity = 0.59 (95% CI: 0.51 to 0.67). Specificity = 0.94 (95% CI: 0.91 to 0.96). PPV = 0.28 (95% CI: 0.20 to 0.36). NPV = 0.99 (95% CI: 0.98 to 0.99). When the five 'good quality' studies only were included in the analysis values were somewhat higher:- Sensitivity = 0.64 (95% CI: 0.47 to 0.80). Specificity = 0.97 (95% CI: 0.95 to 0.99). PPV = 0.47 (95% CI: 0.29 to 0.64). NPV = 0.99 (95% CI: 0.98 to 0.99). Study heterogeneity was highly significant for almost all indicators in both groups. Linear regression indicates that none of the available independent variables show any significant relation with any of the diagnostic indicators that were studied. DRE is a test with high specificity and high NPVs. False negative results are rare, mainly owing to the unselected nature of the study population and the low prevalence of cancer.	Well conducted systematic review. Validity assessment based on the guidelines of the Cochrane collaboration. <i>Inclusion criteria</i> Yes <i>Literature search</i> Yes <i>Validity assessment</i> Yes <i>Study details</i> Yes <i>Pooling and/or synthesis</i> Yes

Table 2.2: Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) in the staging of patients with urological cancers

Study Country Grade	Aims	Methods	Results	Comments
Cancer of the prostate				
Egawa, 1994. ¹⁷ Japan IV	To compare the diagnostic usefulness of imaging modalities in the differentiation of Stage B from Stage C Prostate Cancer.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 18.</p> <p><i>Patient information</i> Men who had radical retropubic prostatectomy for cancer of the prostate were included in the study. All patients had radical retropubic prostatectomy.</p> <p><i>Methods</i> Patients had DRE, transrectal ultrasound, CT and MRI prior to surgery. The radiological report on the images were compared with the pathological report given following the prostatectomy.</p> <p>The TNM system was used to assess the clinical stage of the tumour following DRE.</p> <p>No information is given on how the diagnostic images were interpreted.</p> <p><i>Period</i> Not stated.</p> <p><i>Statistical methods</i> Diagnostic indices.</p>	<p><i>Detection of extra-capsular spread</i></p> <p>Sensitivity:- CT: 8.3% MRI: 61.5%.</p> <p>Specificity:- CT: 100% MRI: 60.0%.</p> <p>Accuracy:- CT: 35.2% MRI: 61.1%.</p> <p>PPV:- CT: 100% MRI: 80.0%.</p> <p>NPV:- CT: 31.2% MRI: 62.5%.</p> <p><i>Detection of invasion of the seminal vesicles</i></p> <p>Sensitivity:- CT: 33.3% MRI: 70.0%.</p> <p>Specificity:- CT: 100% MRI: 75.0%.</p> <p>Accuracy:- CT: 64.7% MRI: 72.2%.</p> <p>PPV:- CT: 100% MRI: 77.7%.</p> <p>NPV:- CT: 57.1% MRI: 66.7%.</p> <p><i>Detection of lymph node involvement</i></p> <p>Sensitivity:- CT: 20.0% MRI: 16.7%.</p> <p>Specificity:- CT: 75.0% MRI: 100%.</p> <p>Accuracy:- CT: 58.8% MRI: 72.2%.</p> <p>PPV:- CT: 25.0% MRI: 100%.</p> <p>NPV:- CT: 69.2% MRI: 70.5%.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Hammerer, 1992. ¹³ Germany IV	To assess the value of various staging interventions, including CT and MRI, in men with prostate cancer.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 103.</p> <p><i>Patient information</i> This study included men who had localised histologically proven cancer of the prostate and who had pelvic retroperitoneal lymphadenectomy.</p> <p><i>Methods</i> All patients had DRE, serum PSA levels, transrectal ultrasound, bone scans, chest radiography and excretory urography. Cross sectional images were obtained prior to prostatectomy. The radiological reports on the images were compared with the pathological report given following prostatectomy. The Whitmore Jewitt staging system was used to assess the clinical stage. Information on the method of interpreting the diagnostic images was not given.</p> <p><i>Period</i> 1988 to 1990.</p> <p><i>Statistical methods</i> Diagnostic indices.</p>	<p>63 patients underwent CT while 52 men had MRI. 91 men had radical prostatectomy.</p> <p><i>Lymph node involvement</i></p> <p>Sensitivity:- CT: 6.7% MRI: 50.0%.</p> <p>Specificity:- CT: 95.8% MRI: 100%.</p> <p>Accuracy:- CT: 74.6% MRI: 86.5%.</p> <p>PPV:- CT: 33.3% MRI: 100%.</p> <p>NPV:- CT: 76.7% MRI: 84.4%.</p> <p><i>Seminal vesicle invasion</i></p> <p>Sensitivity:- CT: 25.0% MRI (T1): 45.4%.</p> <p>Specificity:- CT: 92.0% MRI (T1): 97.5%.</p> <p>Accuracy:- CT: 79.0% MRI (T1): 86.5%.</p> <p>PPV:- CT: 42.9% MRI (T1): 83.3%.</p> <p>NPV:- CT: 83.6% MRI (T1): 86.9%.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Cancer of the bladder				
Benz, 1992. ¹² Germany IV	To compare the effectiveness of CT and MRI in the staging of bladder cancer.	<p><i>Diagnosis</i> Bladder cancer.</p> <p><i>Number of patients</i> 22.</p> <p><i>Patient information</i> Patients in whom a diagnosis of bladder tumour was suspected were investigated in this study. Information is presented on those in whom histological verification was obtained. 28 patients had clinical suspicion of Bladder cancer, 22 had this suspicion pathologically confirmed.</p> <p><i>Methods</i> This study was conducted prospectively. All patients had preoperative CT, MRI and isotope imaging. Staging information was obtained using the TNM system. Patients proceeded to have cystectomy and histological confirmation of diagnosis and staging was obtained and compared with the imaging reports. No information was presented on the process of interpretation of the images.</p> <p><i>Period</i> August 1990 to July 1991.</p> <p><i>Statistical methods</i> Descriptive.</p>	<p>All patients had a MRI scan but three patients did not undergo a CT scan.</p> <p><i>Perivesicular invasion</i> Understaged:- MRI - 0 of 5 CT - 0 of 2. Accurately staged:- MRI - 3 of 5 CT - 2 of 2. (i.e. Accuracy:- MRI - 60% CT - 100%). Overstaged:- MRI - 2 of 5 CT - 0 of 2.</p> <p><i>Infiltration of the seminal vesicles or uterus</i> Understaged:- MRI - 0 of 5 CT - 3 of 6. Accurately staged:- MRI - 3 of 5 CT - 3 of 6. (i.e. Accuracy:- MRI - 60% CT - 50%). Overstaged:- MRI - 2 of 5 CT - 0 of 6.</p> <p><i>Identification of involved lymph nodes</i> Understaged:- MRI - 0 of 5 CT - 3 of 5. Accurately staged:- MRI - 3 of 5 CT - 2 of 5. (i.e. Accuracy:- MRI - 60% CT - 40%). Overstaged:- MRI - 2 of 5 CT - 0 of 5.</p> <p><i>Identification of distant metastases</i> Understaged:- MRI - 0 of 1. Accurately staged:- MRI - 0 of 1. Overstaged:- MRI - 1 of 1.</p> <p><i>Total staging of disease</i> Understaged:- MRI - 0% CT - 22%. Accurately staged:- MRI - 75% CT - 63%. Overstaged:- MRI - 25% CT - 15%</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Kim, 1994. ⁹ USA IV	To evaluate the accuracy of contrast material enhanced CT, unenhanced T1 and T2 weighted MRI and dynamic gadolinium enhanced spoiled gradient echo MRI in the staging of cancer of the bladder.	<p><i>Diagnosis</i> Bladder cancer.</p> <p><i>Number of patients</i> 36.</p> <p><i>Patient information</i> Patients with biopsy confirmed cancer of the bladder were included in the study. All patients had histological confirmation.</p> <p>33 patients were diagnosed with transitional cell carcinoma of the bladder (TCC), 2 patients had squamous cell carcinoma (SCC) and one patient had an adenocarcinoma (ACa) of the bladder.</p> <p><i>Methods</i> Patients were referred for CT and MRI imaging within 3 weeks of their biopsy. They proceeded to have either to have cystectomy or transurethral resection of their tumour (with additional staging biopsies), giving pathological verification of the staging information, within 11 days of the second imaging procedure. A comparison was made between staging information from imaging and histological sources.</p> <p>No information is given on the process of interpretation of the diagnostic images.</p> <p><i>Period</i> Not stated.</p> <p><i>Statistical methods</i> Diagnostic indices.</p>	<p><i>Diagnosis with enhanced CT</i> Sensitivity:- 93%. PPV:- 96%.</p> <p><i>Diagnosis with T1 weighted MRI</i> Sensitivity:- 91%. PPV:- 94%.</p> <p><i>Diagnosis with T2 weighted MRI</i> Sensitivity:- 94%. PPV:- 94%.</p> <p><i>Diagnosis with dynamic gadolinium enhanced spoiled GRE imaging</i> Sensitivity:- 100%. PPV:- 93%.</p> <p><i>Diagnosis with late gadolinium enhanced T1 weighted imaging</i> Sensitivity:- 94%. PPV:- 94%.</p> <p><i>Staging with enhanced CT</i> Understaged:- 3 of 29 (10%). Accurately staged:- 16 of 29 (55%). Overstaged:- 10 of 29 (34%).</p> <p><i>Staging with T1 weighted MRI</i> Understaged:- 8 of 36 (22%). Accurately staged:- 16 of 36 (44%). Overstaged:- 12 of 36 (33%).</p> <p><i>Staging with T2 weighted MRI</i> Understaged:- 5 of 36 (14%). Accurately staged:- 22 of 36 (61%). Overstaged:- 9 of 36 (25%).</p> <p><i>Staging with dynamic gadolinium enhanced spoiled GRE imaging</i> Understaged:- 2 of 27 (7%).</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments																		
			<p>Accurately staged:- 18 of 27 (67%). Overstaged:- 7 of 27 (26%).</p> <p><i>Staging with late gadolinium enhanced T1 weighted imaging</i> Understaged:- 1 of 36 (3%). Accurately staged:- 23 of 36 (64%). Overstaged:- 12 of 36 (33%).</p> <p><i>Overall staging with MRI</i> Understaged:- 0 of 36. Accurately staged:- 27 of 36 (75%). Overstaged:- 9 of 36 (25%).</p> <p><i>Staging accuracies of MRI and CT</i></p> <table border="0"> <tr> <td>pT0</td> <td>Overall MRI - 0 of 2</td> <td>CT - 0 of 1.</td> </tr> <tr> <td>PTa to pT1</td> <td>Overall MRI - 1 of 3 (33%)</td> <td>CT - 0 of 3.</td> </tr> <tr> <td>pT2</td> <td>Overall MRI - 5 of 9 (56%)</td> <td>CT - 3 of 7 (43%).</td> </tr> <tr> <td>pT3a</td> <td>Overall MRI - 3 of 4 (75%)</td> <td>CT - 0 of 2.</td> </tr> <tr> <td>pT3b</td> <td>Overall MRI - 12 of 12 (100%)</td> <td>CT - 10 of 12 (83%).</td> </tr> <tr> <td>pT4</td> <td>Overall MRI - 6 of 6 (100%)</td> <td>CT - 3 of 4 (75%)</td> </tr> </table>	pT0	Overall MRI - 0 of 2	CT - 0 of 1.	PTa to pT1	Overall MRI - 1 of 3 (33%)	CT - 0 of 3.	pT2	Overall MRI - 5 of 9 (56%)	CT - 3 of 7 (43%).	pT3a	Overall MRI - 3 of 4 (75%)	CT - 0 of 2.	pT3b	Overall MRI - 12 of 12 (100%)	CT - 10 of 12 (83%).	pT4	Overall MRI - 6 of 6 (100%)	CT - 3 of 4 (75%)	
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pT3b	Overall MRI - 12 of 12 (100%)	CT - 10 of 12 (83%).																				
pT4	Overall MRI - 6 of 6 (100%)	CT - 3 of 4 (75%)																				
Mohri, 1995. ¹⁹ Japan IV	To assess diagnostic efficacy of CT and MRI in the staging of bladder cancers.	<p><i>Diagnosis</i> Bladder cancer.</p> <p><i>Number of patients</i> 18.</p> <p><i>Patient information</i> Patients with cancers of the urinary bladder were included in the review. 16 patients had TCC bladder, one had predominantly TCC with some SCC and one patient had signet ring cell carcinoma.</p> <p><i>Methods</i> Patients were referred for CT and for dynamic MRI enhanced by the use of Gadolinium contrast media. Staging information was collected from the radiological reports. The TNM staging system was used.</p> <p>Patients preceded to have resection of their</p>	<p>Both CT and MRI reported some patients as Stage 'Less than or equal to 2'. The following figures include this as staged accurately.</p> <table border="0"> <tr> <td>Understaged:-</td> <td>MRI - 2 of 18 (11.1%)</td> <td>CT - 4 of 18 (22.2%).</td> </tr> <tr> <td>Accurately staged:-</td> <td>MRI - 12 of 18 (66.7%)</td> <td>CT - 10 of 18 (55.6%).</td> </tr> <tr> <td>Overstaged:-</td> <td>MRI - 4 of 18 (22.2%)</td> <td>CT - 4 of 18 (22.2%)</td> </tr> </table>	Understaged:-	MRI - 2 of 18 (11.1%)	CT - 4 of 18 (22.2%).	Accurately staged:-	MRI - 12 of 18 (66.7%)	CT - 10 of 18 (55.6%).	Overstaged:-	MRI - 4 of 18 (22.2%)	CT - 4 of 18 (22.2%)	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i></p>									
Understaged:-	MRI - 2 of 18 (11.1%)	CT - 4 of 18 (22.2%).																				
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Study Country Grade	Aims	Methods	Results	Comments
		<p>tumours with histopathological examination of the specimen. The results of the pathological diagnosis and staging were compared with the diagnosis and staging information obtained using the imaging modalities.</p> <p><i>Period</i> Not stated.</p> <p><i>Statistical methods</i> Descriptive.</p>		<p>Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>
<p>Pagliarulo, 1993.¹⁶</p> <p>Italy</p> <p>IV</p>	<p>To evaluate the accuracy of CT and MRI in the staging of Bladder cancer.</p>	<p><i>Diagnosis</i> Bladder cancer.</p> <p><i>Number of patients</i> 23.</p> <p><i>Patient information</i> Patients who were referred for radical resection of a bladder tumour were evaluated in this series. All patients had radical cystectomy and pelvic lymphadenopathy.</p> <p><i>Methods</i> Patients underwent pre-operative CT and MRI imaging. All patients proceeded to undergo cystectomy.</p> <p>Results of the imaging procedures were compared with the histological reports obtained during the resection of the tumour.</p> <p>The TNM system was used to assess the extent of the primary and lymph node disease.</p> <p>No information is given about the process of interoperation of the diagnostic images.</p> <p><i>Period</i> January 1991 to December 1992.</p> <p><i>Statistical methods</i> Descriptive.</p>	<p><i>Identification of disease confined to the bladder wall (T1 to T3a)</i> Understaged:- MRI - 0 of 12 CT - 0 of 12. Accurately staged:- MRI - 8 of 12 (66.6%) CT - 10 of 12 (83.3%). Overstaged:- MRI - 4 of 12 (33.3%) CT - 2 of 12 (16.6%).</p> <p><i>Identification of disease invading the perivesicular fat (T3b)</i> Understaged:- MRI - 2 of 7 (28.6%) CT - 3 of 7 (42.9%). Accurately staged:- MRI - 5 of 7 (71.4%) CT - 4 of 7 (57.1%). Overstaged:- MRI - 0 of 7 CT - 0 of 7.</p> <p><i>Identification of disease invading adjacent structures (T4)</i> Understaged:- MRI - 3 of 4 (75%) CT - 3 of 4 (75%). Accurately staged:- MRI - 1 of 4 (25%) CT - 1 of 4 (25%). Overstaged:- MRI - 0 of 4 CT - 0 of 4.</p> <p><i>Detection of nodal involvement</i> Understaged:- MRI - 2 of 4 (50%) CT - 2 of 4 (50%). Accurately staged:- MRI - 2 of 4 (50%) CT - 2 of 4 (50%). Overstaged:- MRI - 0 of 4 CT - 0 of 4</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments																																																																						
Cancer of the kidney																																																																										
Boyer, 1995. ¹⁸ France IV	To evaluate CT and MRI scanning in the pre-operative evaluation of renal tumours.	<p><i>Diagnosis</i> Kidney cancer.</p> <p><i>Number of patients</i> 46.</p> <p><i>Patient information</i> Patients with solid kidney tumours who underwent MRI and CT imaging prior to radical resection of their tumour were included.</p> <p><i>Methods</i> Two radiologist retrospectively re-evaluated the CT and MRI images using a defined set of diagnostic imaging criteria. These results were compared with the pathological report given following the resection of the kidney tumour. The TNM system was used to stage the tumour in each case. Data were assessed in terms of capsular breach, invasion of peri-renal structures, lymphatic spread and venous extension.</p> <p><i>Period</i> Not stated.</p> <p><i>Statistical methods</i> Diagnostic indices.</p>	<p>All patients underwent MRI while 43 patients (93.4%) had CT as well.</p> <p><i>Capsular breach</i></p> <table border="0"> <tr> <td>Sensitivity:-</td> <td>MRI: 95.7%</td> <td>CT: 95.2%.</td> </tr> <tr> <td>Specificity:-</td> <td>MRI: 52.2%</td> <td>CT: 40.0%.</td> </tr> <tr> <td>Accuracy:-</td> <td>MRI: 73.9%</td> <td>CT: 68.4%.</td> </tr> <tr> <td>PPV:-</td> <td>MRI: 66.7%</td> <td>CT: 62.5%.</td> </tr> <tr> <td>NPV:-</td> <td>MRI: 92.3%</td> <td>CT: 88.9%.</td> </tr> </table> <p><i>Invasion of the peri-nephric fat</i></p> <table border="0"> <tr> <td>Sensitivity:-</td> <td>T1: 100%</td> <td>CT: 66.7%.</td> </tr> <tr> <td>Specificity:-</td> <td>T1: 55.8%</td> <td>CT: 60.0%.</td> </tr> <tr> <td>Accuracy:-</td> <td>T1: 58.7%</td> <td>CT: 60.5%.</td> </tr> <tr> <td>PPV:-</td> <td>T1: 13.6%</td> <td>CT: 11.1%.</td> </tr> <tr> <td>NPV:-</td> <td>T1: 100%</td> <td>CT: 96.0%.</td> </tr> </table> <p><i>Invasion of the peri-nephric organs</i></p> <table border="0"> <tr> <td>Sensitivity:-</td> <td>T1: 100%</td> <td>CT: 33.3%.</td> </tr> <tr> <td>Specificity:-</td> <td>T1: 97.7%</td> <td>CT: 100%.</td> </tr> <tr> <td>Accuracy:-</td> <td>T1: 97.8%</td> <td>CT: 95.3%.</td> </tr> <tr> <td>PPV:-</td> <td>T1: 75.0%</td> <td>CT: 100%.</td> </tr> <tr> <td>NPV:-</td> <td>T1: 100%</td> <td>CT: 95.2%.</td> </tr> </table> <p><i>Lymphatic spread</i></p> <table border="0"> <tr> <td>Sensitivity:</td> <td>MRI: 71.4%-</td> <td>CT: 57.1%.</td> </tr> <tr> <td>Specificity:-</td> <td>MRI: 92.3%</td> <td>CT: 88.9%.</td> </tr> <tr> <td>Accuracy:-</td> <td>MRI: 89.1%</td> <td>CT: 83.7%.</td> </tr> <tr> <td>PPV:-</td> <td>MRI: 62.5%</td> <td>CT: 50.0%.</td> </tr> <tr> <td>NPV:-</td> <td>MRI: 94.7%</td> <td>CT: 91.4%.</td> </tr> </table> <p><i>Extension to the proximal renal vein</i></p> <table border="0"> <tr> <td>Sensitivity:-</td> <td>T1: 78.6%</td> <td>FLASH: 71.4%</td> <td>FLASH T1: 78.6%</td> <td>CT: 83.3%.</td> </tr> <tr> <td>Specificity:-</td> <td>T1: 96.9%</td> <td>FLASH: 96.6%</td> <td>FLASH T1: 96.9%</td> <td>CT: 83.9%.</td> </tr> </table>	Sensitivity:-	MRI: 95.7%	CT: 95.2%.	Specificity:-	MRI: 52.2%	CT: 40.0%.	Accuracy:-	MRI: 73.9%	CT: 68.4%.	PPV:-	MRI: 66.7%	CT: 62.5%.	NPV:-	MRI: 92.3%	CT: 88.9%.	Sensitivity:-	T1: 100%	CT: 66.7%.	Specificity:-	T1: 55.8%	CT: 60.0%.	Accuracy:-	T1: 58.7%	CT: 60.5%.	PPV:-	T1: 13.6%	CT: 11.1%.	NPV:-	T1: 100%	CT: 96.0%.	Sensitivity:-	T1: 100%	CT: 33.3%.	Specificity:-	T1: 97.7%	CT: 100%.	Accuracy:-	T1: 97.8%	CT: 95.3%.	PPV:-	T1: 75.0%	CT: 100%.	NPV:-	T1: 100%	CT: 95.2%.	Sensitivity:	MRI: 71.4%-	CT: 57.1%.	Specificity:-	MRI: 92.3%	CT: 88.9%.	Accuracy:-	MRI: 89.1%	CT: 83.7%.	PPV:-	MRI: 62.5%	CT: 50.0%.	NPV:-	MRI: 94.7%	CT: 91.4%.	Sensitivity:-	T1: 78.6%	FLASH: 71.4%	FLASH T1: 78.6%	CT: 83.3%.	Specificity:-	T1: 96.9%	FLASH: 96.6%	FLASH T1: 96.9%	CT: 83.9%.	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>
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Constantinides, 1991. ¹⁰ Switzerland IV	To evaluate the accuracy of CT and MRI in the staging of patients investigated for renal cell carcinoma (RCC).	<i>Diagnosis</i> RCC. <i>Number of patients</i> 68. <i>Patient information</i> Data from patients with renal cell carcinoma who underwent radical nephrectomy were evaluated. <i>Methods</i> All patients underwent pre-operative CT, angiography and MRI. Each modality was performed and interpreted by different professionals and each professional was unaware of the results of the other modality. TNM staging was used to stage the extent of disease. The extent of venous disease (V Stage) was also recorded. Results of the imaging modalities were compared with the operative and histopathological findings,	<i>T Stage</i> Understaged:- MRI - 1 of 27 (4.3%) CT - 5 of 39 (12.8%). Accurately staged:- MRI - 17 of 27 (62.9%) CT - 25 of 39 (64.1%). Overstaged:- MRI - 9 of 27 (33.3%) CT - 9 of 39 (23.1%). <i>N Stage</i> Understaged:- MRI - 1 of 27 (3.7%) CT - 3 of 39 (7.7%). Accurately staged:- MRI - 24 of 27 (88.9%) CT - 30 of 39 (76.9%). Overstaged:- MRI - 2 of 27 (7.4%) CT - 6 of 39 (15.4%). <i>V Stage</i> Understaged:- MRI - 10 of 27 (37.0%) CT - 9 of 39 (23.1%). Accurately staged:- MRI - 17 of 27 (63.0%) CT - 29 of 39 (74.4%). Overstaged:- MRI - 0 of 27 (0%) CT - 1 of 39 (2.6%)	Grade <i>Population</i> Pass <i>Reference</i> Pass <i>Blinding</i> Not stated <i>Case control</i> Pass Quality <i>Sample</i> Pass <i>Inclusions</i> Pass <i>Entry point</i>

Study Country Grade	Aims	Methods	Results	Comments
		<p>which were accepted as the gold standard.</p> <p><i>Period</i> 1986 to 1987.</p> <p><i>Statistical methods</i> Descriptive.</p>		<p>Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>
<p>De Cobelli, 1993.¹⁵</p> <p>Italy</p> <p>IV</p>	<p>Evaluating the accuracy of contrast enhanced CT, MRI and contrast enhanced MRI in the staging of renal cell carcinomas.</p>	<p><i>Diagnosis</i> RCC.</p> <p><i>Number of patients</i> 44.</p> <p><i>Patient information</i> Patients with renal cell carcinoma who were referred for surgical resection were included in this study.</p> <p><i>Methods</i> This study was conducted prospectively. Patients were referred for CT and for unenhanced and contrast enhanced MRI prior to surgery. The images were interpreted by three radiologists independently. Patients had resection of their tumours and histopathological verification of the stage was obtained. Comparison of the imaging and operative staging results was performed. The Robson (1969) system of staging was used.</p> <p><i>Period</i> January 1991 to March 1992.</p> <p><i>Statistical methods</i> Descriptive.</p>	<p>Understaged:- MRI - 0 MRI (with CM) - 0 CT - 0.</p> <p>Accurately staged:- MRI - 36 (81.8%) MRI (with CM) - 39 (88.6%) CT - 36 (81.8%).</p> <p>Overstaged:- MRI - 8 (18.2%) MRI (with CM) - 5 (11.4%) CT - 8 (18.2%)</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Hallscheidt, 1998. ²⁰ Germany IV	To evaluate the accuracy of CT and MRI in staging RCC.	<p><i>Diagnosis</i> RCC.</p> <p><i>Number of patients</i> 33.</p> <p><i>Patient information</i> Patients who had both MRI and CT scanning prior to either a nephrectomy or enucleation of a cancer of the kidney, which provided histological confirmation of diagnosis and staging, were included in this review. Patients who were inoperable or who were unable to undergo the imaging investigations were excluded.</p> <p><i>Methods</i> This study was conducted prospectively. Patients were referred to have CT and MRI scanning and staging information was recorded. The TNM system was utilised.</p> <p>Patients proceeded to have radical surgery and pathological confirmation and staging was obtained. Results of the imaging and operative staging were compared.</p> <p><i>Period</i> June 1995 to March 1996.</p> <p><i>Statistical methods</i> Descriptive.</p>	<p><i>T Stage</i> Understaged:- MRI - 2 (6.1%) CT - 3 (9.1%). Accurately staged:- MRI - 28 (84.8%) CT - 27 (81.8%). Overstaged:- MRI - 3 (9.1%) CT - 3 (9.1%).</p> <p><i>N Stage</i> Understaged:- MRI - 2 (6.1%) CT - 4 (12.1%). Accurately staged:- MRI - 29 (87.9%) CT - 26 (78.1%). Overstaged:- MRI - 1 (3.0%) CT - 4 (12.1%).</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>
Kirkali, 1994. ⁸ Turkey IV	To evaluate the place of MRI in the staging of renal cell carcinoma by comparing with CT staging and histopathological results.	<p><i>Diagnosis</i> RCC.</p> <p><i>Number of patients</i> 25.</p> <p><i>Patient information</i> All patients who were diagnosed with a tumour of the kidney following a CT examination and who had histological confirmation of their diagnosis, were further investigated with MRI scanning. All patients studied had both CT and MRI and</p>	<p>MRI staged 23 of 25 patients (92%) accurately. CT staged only 19 of 25 patients (76%) accurately. In three cases, a tumour in the upper pole of the kidney was overstaged by CT which was suspicious of hepatic involvement. In all three cases, MRI correctly staged these patients.</p> <p>Sagittal images, possible in MRI but not at that time with CT, proved helpful in a number of cases, including in identifying vertebral metastases in one case. One patient had metastatic liver disease which was identified by MRI but not by CT. MRI and CT both failed to identify microscopic extra-capsular extension in two cases.</p> <p>Both modalities identified lymphatic involvement in 3 patients (12%).</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p>

Study Country Grade	Aims	Methods	Results	Comments
		<p>subsequently had radical nephrectomy.</p> <p><i>Methods</i> Patients underwent CT scanning and if a kidney tumour was visualised, were referred for MRI scanning. Appropriate patients were referred for radical nephrectomy.</p> <p>Data were collected from all images by one radiologist in a radiological review. He was 'blinded' to the imaging report of the other modality and to the pathological findings.</p> <p>Review findings and pathological findings were compared.</p> <p><i>Period</i> Not stated.</p> <p><i>Statistical methods</i> Descriptive.</p>		<p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>
<p>Krestin, 1992.¹⁴ Germany, Switzerland IV</p>	<p>To evaluate the use of MRI (in comparison with CT) in the staging of RCC.</p>	<p><i>Diagnosis</i> RCC.</p> <p><i>Number of patients</i> 79.</p> <p><i>Patient information</i> Patients who had renal cell carcinoma were included in this study.</p> <p><i>Methods</i> Patients underwent pre-operative CT and MRI imaging. All patients proceeded to undergo resection of their tumour(s).</p> <p>Results of the imaging procedures were compared with the histological reports obtained during the resection of the tumour.</p> <p>The TNM system was used to assess the extent of the primary and lymph node disease.</p> <p>No information is given about the process of interpretation of the diagnostic images.</p>	<p><i>T stage</i> Understaged:- MRI - 6 (6.8%) CT - 6 (6.8%). Accurately staged:- MRI - 74 (84.1%) CT - 69 (78.4%). Overstaged:- MRI - 8 (9.1%) CT - 13 (14.8%).</p> <p><i>N stage</i> Understaged:- MRI - 8 (9.1%) CT - 8 (9.1%). Accurately staged:- MRI - 70 (79.5%) CT - 72 (81.8%). Overstaged:- MRI - 10 (11.4%) CT - 8 (9.1%)</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p>

Study Country Grade	Aims	Methods	Results	Comments
		<p><i>Period</i> January 1988 to July 1991.</p> <p><i>Statistical methods</i> Descriptive.</p>		<p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>
Kabala, 1991. ¹¹ England V	To examine the role of MRI in the staging of patients with RCC.	<p><i>Diagnosis</i> RCC.</p> <p><i>Number of patients</i> 11.</p> <p><i>Patient information</i> Data from patients who had renal cell carcinoma and who had MRI imaging were evaluated.</p> <p><i>Methods</i> Patients with renal cell carcinoma were referred to undergo MRI imaging. Some additionally had CT imaging. Staging of the disease followed the Robson (1969) method.</p> <p>In patients who were deemed appropriate, radical nephrectomy was performed. The imaging results were compared with the histopathological findings.</p> <p>Not all patients in the series (n = 24) had CT and not all preceded to have surgery. Data were summarised only on those who had all three procedures (MRI, CT, post surgical histological staging).</p> <p>No information on the process of interpretation of the images was given.</p> <p><i>Period</i> Not stated.</p> <p><i>Statistical methods</i> Descriptive.</p>	<p>In 24 patients with renal cell carcinomas, the imaging and pathological agreement was measured. 15 patients, who had pathological confirmation of stage, had MR imaging. 11 of these patients had CT as well.</p> <p>CT resulted in accurate staging estimation for 9 of 11 patients (81.8%) but in over staging in 2 patients (18.2%). No patient was understaged by CT imaging.</p> <p>MRI resulted in accurate staging estimation for 14 of 15 patients (93.3%) but in over staging in 1 patient (6.7%). No patient was understaged by MR imaging.</p> <p>In two patients, apparent invasion of the IVC on CT was demonstrated to be compression of the vessel but with no invasion on the MRI image.</p> <p>In one patient spinal metastatisation was missed by the CT but not the MRI scan.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Fail</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Table 2.3: The efficacy of plain film chest radiography (CXR) in the detection of thoracic metastases in men with testicular tumours: primary studies

Study Country Grade	Aims	Methods	Results	Comments
Buchholz, 1998. ²¹ USA IV	To assess the follow-up pattern of patients treated with orchidectomy and adjuvant radiotherapy in a single institution and to determine the cost-effectiveness of that screening program.	<p><i>Number of patients</i> 58</p> <p><i>Number of patients with seminoma</i> 58</p> <p><i>Number of patients with NSGCT</i> 0</p> <p><i>Additional patient information</i> Men were included in the study if they had seminoma with no disease outside the testis other than infradiaphragmatic nodes of 5 cm maximum dimension or less. All patients underwent an orchidectomy and proceeded to have radiotherapy. Men were excluded from the review if they had less than one year follow-up. 88% of the 58 patients were soldiers on active duty.</p> <p><i>Time period</i> 1988 to 1995.</p> <p><i>Methods</i> All patients had testicular ultrasound, alpha fetoprotein (αFP) and beta human chorionic gonadotrophin (BHCG) prior to orchidectomy. Orchidectomy was followed by radiotherapy to the para-aortic and ipsilateral inguinal nodes with or without radiotherapy to the contralateral inguinal nodes. All patients had post operative abdominopelvic CT and chest radiography.</p> <p>Data were collated retrospectively. No information is given on the process of interpreting the radiographic images.</p> <p><i>Statistical methods</i> Descriptive statistics.</p>	<p>Mean follow-up was 55 months. Patients attended a mean 15 follow-up appointments.</p> <p>There were no deaths in the series.</p> <p>2 of 58 patients (3.5%) had a recurrence; neither was in the radiotherapy field.</p> <p>Patients with raised biochemical markers prior to orchidectomy did not suffer any recurrences in the follow-up period.</p> <p>815 chest radiographs were obtained (mean 14.6 per patient). 8 chest CT's were performed (mean 0.13 per patient).</p> <p>No recurrence was found from routine imaging. Both recurrences were identified following reports of symptoms by the patient and confirmed by subsequent non-scheduled imaging.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Gels, 1995. ²² The Netherlands IV	To examine the adequacy of the 'wait and see' policy for patients with Stage I NSGCT.	<p><i>Number of patients</i> 154</p> <p><i>Number of patients with seminoma</i> 0</p> <p><i>Number of patients with NSGCT</i> 154</p> <p><i>Additional patient information</i> Men with Clinical Stage I NSGCT of the testes were included in the study. All patients had histological confirmation of a diagnosis of NSGCT.</p> <p><i>Time period</i> January 1982 to December 1991.</p> <p><i>Methods</i> Clinical staging was performed using clinical examination, CXR, tumour markers and chest and abdominal CT. Data on the pathological type and the diameter of the tumour were obtained from reports on the surgical specimen.</p> <p>Data were collated retrospectively. No information is given on the process of interpreting the radiographic images.</p> <p><i>Statistical methods</i> Student's t test, χ^2 test, Fischer's exact test, multivariate logistic regression.</p>	<p>During follow-up, 112 patients of 154 patients (72.7%) remained disease free after radical orchidectomy. 42 of 154 patients (27.3%) were diagnosed with metastatic recurrences. Recurrence was diagnosed after a mean duration of 5.7 months (median, 4 months, range 2 to 24 months) of surgery. 38 of 42 (90%) recurrences occurred within one year of orchidectomy and 4 of 42 (10%) occurred between one and two years after orchidectomy. No recurrence occurred more than two years after orchidectomy.</p> <p>13 of 42 patients (31%) of patients with recurrences had intra-thoracic deposits. In four cases (10%) these were the only metastatic deposits. Only one of the patients (8%) who had thoracic disease recurred in the period of one to two years after orchidectomy.</p> <p>In 16 patients (38%) recurrence was identified only by CT scanning. Of these, 5 patients had intra-thoracic metastases. 25 patients (60%) had raised biochemical markers. 17 of these patients had abnormal CT scans. One of 42 patients (2%) had his recurrence identified on clinical examination. No recurrences were identified by plain film chest radiography.</p> <p>In 11 of 13 patients (85%) with intra-thoracic metastases, plain film radiography of the chest did not demonstrate the disease. In the remaining 2 cases (15%), the disease was visible with this modality but had already been diagnosed using another method (CT or tumour markers).</p> <p>40 of 42 patients (95%) who suffered a recurrence went on to achieve remission of their recurrence following platinum-based chemotherapy. One patient attained remission following local excision of a solitary metastasis. The remaining patient refused recommended chemotherapy and subsequently died. One of the patients who had attained remission following chemotherapy developed a second recurrence, received second line chemotherapy but subsequently died.</p> <p>Ultimate disease-free survival was achieved for 152 patients (98.7%). Mean follow-up was 7 years.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Rathmell, 1993. ²³ England IV	To examine the relapse patterns of men with metastatic germ cell tumours of the testis so as to determine the relative effectiveness of clinical follow-up and routine investigations.	<p><i>Number of patients</i> 334</p> <p><i>Number of patients with seminoma</i> 132</p> <p><i>Number of patients with NSGCT</i> 202</p> <p><i>Additional patient information</i> Patients were included in the study if their tumour marker levels reached normal after initial therapy and if they had either no residual mass or any residual mass was stable or decreasing.</p> <p><i>Time period</i> 1979 to 1989.</p> <p><i>Methods</i> Patients had CXR, αFP and β-HCG at every follow-up appointment and chest and abdominal CT scans on a 3 to 4 monthly basis. No information is given on the process of interpreting the radiographic images.</p> <p><i>Statistical methods</i> Descriptive statistics.</p>	<p>29 of 334 patients (8.7%) recurred. Seven of 132 men with seminoma (5.3%) recurred and 22 of 202 men with NSGCT recurred (10.9%).</p> <p>Recurrence was diagnosed in 7% (2/29) of patients following CXR. Both patients relapsed early (within 5 months of remission) and occurred prior to the first scheduled CTC. One of these patients had seminoma and the other had NSGCT.</p> <p>An additional four patients had an abnormal CXR after relapse had been diagnosed by other means.</p> <p>Recurrence was diagnosed in 24% (7/29) of patients following CTC. Five of these patients had NSGCT and two had seminoma. Only two of these investigations was at a planned time. CTC appeared particularly effective at detecting recurrence in patients with residual masses after initial treatment.</p> <p>An additional 19 patients had an abnormal CTC after relapse had been diagnosed by other means.</p> <p>The median time to relapse was 20 weeks for NSGCT and only 5 from 22 patients (23%) relapsed after one year. The median time to relapse for patients with seminoma was 68 weeks and 3 from 7 patients (43%) were within the first year.</p> <p>27 from 29 patients recurred within three years of achieving remission. The remaining two patients, both of whom had NSGCT, relapsed more than eight years after remission was achieved.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Not stated</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Scholeremann, 1996. ²⁴ Germany IV	To present a follow-up programme for germ cell tumours related to the patient's risk of relapse.	<p><i>Number of patients</i> 503</p> <p><i>Number of patients with seminoma</i> 164</p> <p><i>Number of patients with NSGCT</i> 339</p> <p><i>Additional patient information</i> Patients with germ cell tumours of the testes who achieved remission were included in this review. A minimum period of remission of 4 weeks was required. Patients were excluded if they had non-germinal testicular tumours or carcinoma-in-situ. Only those patients with a minimum of one year's follow-up were analysed. 84 of 587 patients were excluded for these reasons.</p> <p><i>Time period</i> 1982 to 1992.</p> <p><i>Methods</i> Clinical information was collected from patients notes and included the clinical condition, serum tumour marker levels, radiological findings and serum sex hormone levels.</p> <p><i>Statistical methods</i> Descriptive statistics.</p>	<p>257 of 503 patients (51.1%) had Stage I disease and 25 men (9.7%) had a recurrence. 4 of 119 men (3.4%) with seminoma had a recurrence while 21 of 138 men with Stage I NSGCT (15.2%) had a recurrence. This group included 26 men who were managed with surveillance. 7 of 26 patients (26.9%) suffered a recurrence.</p> <p>Of 112 men with Stage I disease who had a bilateral retroperitoneal lymphadenectomy, 14 (12.5%) suffered a recurrence.</p> <p>Of 181 men treated for Stage II disease, 7 men (3.9%) had a recurrence. Of 65 men treated for Stage III disease, 2 men (3.1%) had a recurrence.</p> <p>Of 33 recurrences for which data on the date of recurrence was available, 7 (21%) occurred between seven and nine weeks after surgery, 11 (33%) between three and six months after surgery and nine (27%) between seven and 12 months after surgery. A total of 27 from 33 (91%) recurrences occurred in the first year.</p> <p>One recurrence happened in the second year after surgery and two recurrences occurred in the third year after surgery. One recurrence occurred in each of the fourth (3%), fifth (3%) and seventh (3%) years after surgery.</p> <p>16 of 34 patients (47%) had lung metastases. 10 patients (29%) were diagnosed as having recurrent disease following chest radiography and 2 patients (6%) were diagnosed following CT scanning.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Sharir, 1999. ²⁶ Canada IV	To optimise follow-up in patients with Stage I NSGCT of the testis on surveillance.	<p><i>Number of patients</i> 170</p> <p><i>Number of patients with seminoma</i> 0</p> <p><i>Number of patients with NSGCT</i> 170</p> <p><i>Additional patient information</i> Patients who were offered surveillance as a management protocol for Stage I seminoma of the testes, i.e. confined within the tunica albuginea, were included in the review. Patients were excluded if they never achieved normal biochemical marker levels, had chorionocarcinoma of the testes or physician estimation of poor patient compliance.</p> <p><i>Time period</i> December 1980 to February 1996.</p> <p><i>Methods</i> A retrospective review of the clinical notes of patients was conducted. Data on tumour histology, physical examinations, radiological investigations and αFP and β-HCG levels were recorded.</p> <p><i>Statistical methods</i> Descriptive statistics.</p>	<p>Median follow-up was 6.3 years (0.7 months to 14.4 years). 48 from 170 (28.2%) patients had progressive disease. Median time to progression was 6.9 months (range 2.4 to 20.8 months). 38 of 48 (79.2%) recurrences occurred in the first year. No patient relapsed more than two years after his surgery.</p> <p>Raised markers were evident in 34 from 48 patients (70.8%) and were the only indicator of progression in 4 cases (8.3%). Physical examination with history indicated recurrence in 18 from 48 patients (37.5%) and was the only indicator in two patients (4.2%). An abnormal abdomeno-pelvic CT indicated recurrence in 34 from 48 patients (70.8%) and was the only indicator in 10 men (20.8%).</p> <p>Although chest radiography demonstrated recurrence in the cases of 4 men (8.3%), in each case the recurrence was also evident from tumour markers (4 cases), computed tomography (2 cases) and physical examination (1 case).</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
White, 1999. ²⁷ England IV	To evaluate the role of computer tomography of the chest (CTC) and plain film chest radiography (CXR) in the management of patients with testicular germ cell tumours	<p><i>Number of patients</i> 207</p> <p><i>Number of patients with seminoma</i> 92</p> <p><i>Number of patients with NSGCT</i> 115</p> <p><i>Additional patient information</i> Patients with germ cell tumours of the testes were included in the review. Men with extra-gonadal germ cell tumours or with non-germ cell testicular cancer were not analysed.</p> <p><i>Time period</i> 4.5 year period.</p> <p><i>Methods</i> Data were retrospectively obtained from the patients' notes on the clinical presentation, histology, tumour markers and the clinical course of the disease. Original radiological reports were compared with a 'Standard of Reference' report. The 'Standard of Reference' was used as gold standard for comparison with the imaging modalities in the calculation of sensitivity and specificity data. This involved two independent reports of the images and correlation with biochemical, histological and other clinical data to obtain a consensus diagnosis. This was used as histological confirmation of intra thoracic masses was rarely available.</p> <p><i>Statistical methods</i> Diagnostic indices, Kappa statistics.</p>	<p><i>Sensitivity</i> CTC - 0.95 (95% CI: 0.91 to 0.99). CXR - 0.35 (95% CI: 0.25 to 0.45).</p> <p><i>Specificity</i> CTC - 0.97 (95% CI: 0.96 to 0.98). CXR - 0.99 (95% CI: 0.98 to 1.00).</p> <p><i>Accuracy</i> CTC - 0.97 (95% CI: 0.96 to 0.98). CXR - 0.91 (95% CI: 0.89 to 0.93).</p> <p><i>PPV</i> CTC - 0.84 (95% CI: 0.83 to 0.85). CXR - 0.91 (95% CI: 0.89 to 0.93).</p> <p><i>NPV</i> CTC - 0.99 (95% CI: 0.98 to 1.00). CXR - 0.91 (95% CI: 0.89 to 0.93).</p> <p><i>Agreement</i> The CXR report was in agreement with the gold standard in 557 of 612 cases (90.1%). The CTC report was in agreement with the gold standard in 615 of 623 cases (98.7%). The CXR report was in agreement with the CTC report in 541 of 612 cases (88.4%).</p> <p><i>Kappa statistic for agreement with the gold standard</i> CTC - 0.96 (95% CI: 0.95 to 0.97). CXR - 0.65 (95% CI: 0.62 to 0.68).</p> <p><i>Intra-thoracic metastases</i> Intra-thoracic metastasis was more frequent in men with NSGCT (20%) than in men with seminoma (1%, $p < 0.001$). All patients with intra-thoracic metastases also had abdomino-pelvic metastasis.</p> <p><i>Radiation dose</i> The effective dose equivalent for CTC examination ranged from 4.33mSv to 6.5mSv per examination. The combined dose from all CTCs which would normally be expected to be conducted during a follow-up programme was estimated to be 30.31mSv per patient. This is approximately 84 times what would be expected to be absorbed by patients being examined by CXR alone.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Table 2.4: The efficacy of bone scans in the detection of bone metastasis

Study Country Grade	Aims	Methods	Results	Comments
Cancer of the prostate				
Cher, 1998, ⁴⁰ USA IV	To identify clinical parameters that would improve our ability to select patients for bone scanning.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 93.</p> <p><i>Patient information</i> Patients were included if they had increasing PSA levels following radical prostatectomy and bilateral pelvic lymph node dissection.</p> <p>Patients were stratified for analysis on the basis of whether they had received androgen ablation or not. Group 1 Patients had received no ablative therapy while Group 2 (n = 22) had received androgen ablation.</p> <p>The unit of analysis in this study was a follow-up appointment and not a patient. As such, as some patients were scanned more than once, they contribute more than one set of data to the final results.</p> <p><i>Time period</i> 1991 to 1996.</p> <p><i>Methods</i> Bone scans were viewed by a nuclear medicine radiologist, with bone scans which were equivocal being supplemented by additional radiography.</p> <p>Clinical information was obtained from a database of patient information which had been produced prospectively.</p> <p>If raised PSA levels were noted in two or more clinic visits, the patient was judged to have relapsed and the relapse was judged to have occurred on the data of the first raised PSA level.</p> <p>Patients who had undergone androgen ablation were analysed separately.</p> <p><i>Statistical methods</i> Univariate and multivariate logistical regression.</p>	<p>144 bone scans were obtained from 93 patients.</p> <p>122 bone scans were obtained from patients who had received no androgen ablation (Group 1) and 22 bone scans were obtained from men who had received androgen ablation therapy (Group 2).</p> <p>Of 122 consultations in Group 1, 5 (4%) involved bone scans suggestive of malignant disease while 117 of 122 consultations had normal bone scans; three consultations required supplementary images to be obtained prior to final designation of non-malignant status.</p> <p>Of five consultations involving men with bone metastases, 2 were of Gleason grade 7 and the remaining three were of Gleason grade 8 to 10. One man exhibited invasion of the seminal vesicles and one man exhibited extra-capsular extension. The remaining three men developed local nodal involvement. The mean PSA of these five men was 143ng/ml/ml (95% CI: 46.1 to 209). The mean PSA of those who had negative bone scans was 6.2ng/ml (95% CI: 0.05 to 156). This was significant at the 1% level.</p> <p>Raised PSA levels correlated with the likelihood of a positive bone scan in both univariate regression (p = 0.0003) and multivariate regression (p = 0.01). No other factor was significantly associated with the likelihood of having metastatic disease on the bone scan.</p> <p>Based on a logistic regression model, there was a 1% probability of having bone metastases in a patient with a PSA level of 10ng/ml or less.</p> <p>Of consultations analysed in group 2, 6 of 22 (27.3%) with raised PSA had bone metastases. The lowest PSA seen in a man with metastatic disease was 15.47ng/ml. Mean PSA values were lower in men without metastatic disease, 3 (95% CI: 0.05 to 28.3) than in those men with metastatic disease, 383ng/ml (95% CI: 15.5 to 999). PSA levels were lower in men in group 2 than in group 1, irrespective of metastatic status.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated.</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> Pass</p>

Study Country Grade	Aims	Methods	Results	Comments
Gerber, 1991, ³⁰ USA IV	To determine the accuracy of using a combination of serum acid and alkaline phosphatase levels and bone pain could identify patients with prostate cancer who would benefit from a bone scan as part of their initial staging process.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 280.</p> <p><i>Patient information</i> All patients who had treatment for prostate cancer during the study period were included.</p> <p><i>Time period</i> 1983 to 1990.</p> <p><i>Methods</i> Medical records for all patients were reviewed and serum alkaline phosphatase (AlkP), total serum acid phosphatase (TAP) and prostatic fraction of acid phosphatase (PAP) recorded.</p> <p>Reports of bone pain and the diagnosis of bone metastases were also recorded. The bone scan was used as the gold standard in this study without comparison with clinical data.</p> <p>Data relating to their initial consultations were obtained.</p> <p>Normal values for each biochemical level were established for each lab used in the participating centres.</p> <p>All bone scans were reviewed by a nuclear medicine physician with plain films requested as required. Uncertain diagnoses of bone metastases were resolved by the radiologist and urologist by discussion, at which stage all clinical details were available.</p> <p>Patients were placed in one of two groups; those with normal markers and no pain and those with both/either abnormal markers and/or pain. The measurement of pain was subjective – not all patients report pain and some doctors may not record it in the notes.</p> <p>Patients were deemed to have a suspicion of bone metastasis if they had one or more abnormal biochemical result or if they had bone pain. Only if all results were normal and the patient reported no pain was he not suspected of having metastases. In cases of incomplete data, if existing data were abnormal, the patient was evaluated. If all of the available data were normal, the missing information may or may not lead to the patient being categorised as suspicious; as such data on these patients were excluded</p>	<p>288 patients were diagnosed with cancer of the prostate in the participating centres during the study time. 6 patients were clinical Stage A1 and required no further treatment. 4 patients refused participation and the records of one patient were lost. Therefore 277 patients were studied (96.2%).</p> <p>64 from 280 patients (23%) had metastatic disease. Data were complete for 74% of patients who had bone metastases diagnosed (45/64) and for 74% of those who were free of metastases (159/216). 234 of 288 patients were evaluable. 54 patients were excluded from the evaluation because their data were incomplete and normal. However, 2 of these patients had diagnosed bone metastases.</p> <p>The sensitivity of the combined test was 97% (57/59). In the 'worst case scenario', if the two patients with missing data who had bone metastases had been false negatives, the sensitivity would have been 93% (57/61).</p> <p>The specificity of the combined test as a predictor of bone metastases was 63% (136/216). The PPV was 59% (57/96). The NPV was 99% (136/138) but in the worst case scenario would have fallen to 97% (136/140). The accuracy of the combined test was 82% (193/234) which was unchanged in the worst case scenario (193/236).</p> <p>All those patients with diagnosed metastatic bone disease for whom a PSA level is available had a PSA in excess of 25ng/ml.</p> <p>The PPV of various cut points were as follows:- 10ng/ml 27% (13/48), 20ng/ml 35% (13/37) and 25ng/ml 41% (13/32).</p> <p>The NPV for all three cut points was 100%.</p> <p>Of those with normal biochemical markers and no bone pain, only 1.4% (2/138) had evidence of a metastatic deposit on their bone scan.</p> <p>22 of 65 patients (34%) with bone metastasis and 58 of 216 patients (27%) who had no bone metastases required additional diagnostic testing to determine the nature MRI's and of abnormalities discovered on bone scanning. 79 plain film radiographs, 6 CT's, 3 MRI's and 3 bone biopsies were performed in patients who were proven not to have bone metastases. 51 plain film radiographs and 2 MRI scans were conducted in the patients who were determined to have metastatic deposits.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
		<p>were excluded.</p> <p>There are quite a lot of missing data referred to but not in the group of patients who had metastases diagnosed.</p> <p><i>Statistical methods</i> Descriptive statistics.</p>		
<p>Gleave, 1996.²⁹ Canada IV</p>	<p>To determine whether pre-treatment serum prostate-specific antigen (PSA) levels in newly diagnosed prostate cancer patients can identify a group with a low probability of osseous metastasis and safely eliminate the need for a bone scan as a routine part of the staging evaluation.</p>	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 490.</p> <p><i>Patient information</i> Men with newly diagnosed cancer of the prostate were studied. Patients with no current PSA or no information on tumour staging or Gleason scores were excluded.</p> <p><i>Time period</i> January 1990 to June 1993.</p> <p><i>Methods</i> Bone scans – two nuclear medicine physicians read the bone scans independently and resolved differences by discussion. If they failed to reach agreement, a third physician decided. Scans were recorded as positive, negative or indeterminate. Patients with indeterminate results were further investigated with planar radiography. The third physician resolved cases which were still indeterminate once the radiographs had been viewed.</p> <p>All doctors were unaware of the results of the PSA testing, of the tumour grade and of the Gleason Score.</p> <p>The review of patients notes was conducted retrospectively.</p> <p><i>Statistical methods</i> Descriptive statistics.</p>	<p>683 bone scans were evaluated from 490 patients with prostate cancer (Mean age 69.3 years (39 to 100)).</p> <p>28 of 490 patients (6%) had bone scans positive for malignancy at time of diagnosis.</p> <p>While there was a general increase in the PSA level with increasing grade and stage, there was significant overlap between adjacent strata; the PSA level is therefore unsuitable for grading or staging purposes.</p> <p>Bone metastases were more common in Stage T3 patients; 5% of T1 patients, 1% of T2 patients and 18% of T3 patients showed metastatic deposits on bone scans. Metastatisation was more common in less well differentiated tumours; 1.5% of patients with Gleason grade 2 to 4, 3% of patients with Gleason grade 5 to 7 and 18% of patients with Gleason grades 8 to 10.</p> <p>The mean PSA for those patients with nodal metastases only was 20ng/ml and for those men with extra-nodal metastases was 96ng/ml.</p> <p>Of 290 patients with PSA levels below 10ng/ml, none had deposits demonstrated on bone scans. Of those with PSA levels between 10 and 20ng/ml, 4 of 88 patients (4.5%) were diagnosed with bone metastases. Of 64 patients with PSA levels between 20 and 50ng/ml, 24 or 8% had metastases and of the remaining 48 patients with PSA levels above 50ng/ml, 19 or 40% had active bone disease.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Haukaas, 1997. ⁴⁴ Norway IV	To evaluate the utility of bone scans in the assessment of newly diagnosed untreated prostate cancer.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 128.</p> <p><i>Patient information</i> Patients with untreated cancer and with PSA levels and bone scans as part of the initial diagnostic assessment of the disease were included.</p> <p><i>Time period</i> 1987 to 1991.</p> <p><i>Methods</i> The clinical stage was assessed by a urologist using the TNM staging system. The grade was assessed by a pathologist using the WHO classification. Bone scans were assessed by a nuclear medicine physician and equivocal findings were resolved with additional radiography. PSA assays were conducted in a laboratory which had an upper limit of normal at 3ng/ml. Information was collated retrospectively.</p> <p><i>Statistical methods</i> The 2 sample T test, Pearson's correlation co-efficient, Logistic regression, Kaplan Meier survival analysis and Multivariate Cox Regression.</p>	<p>50 patients (39%) had WHO grade 1 disease, 57 patients (45%) had WHO grade 2 disease and 21 patients (16%) had WHO grade 3 disease.</p> <p>49 patients (38%) had disease confined to the organ (i.e. T 1 to 2). The remaining 79 patients (62%) had disease which had spread beyond the prostate.</p> <p>48 patients (38%) had bone scans suggestive of malignancy. 80 patients (62%) had normal bone scans.</p> <p>Of those patients whose bone scans highlighted solitary lesions, only 4% were subsequently found to have metastatic deposits.</p> <p>There was a correlation between the PSA values and the severity of disease on bone scans ($R^2 = 0.636$, $p < 0.01$).</p> <p>No patient with PSA below 10ng/ml were found to have metastatic deposits. Only 3 of 41 patients (7%) with PSA levels between 10 and 20ng/ml had metastatic disease.</p> <p>Multivariate regression identified PSA (at 20ng/ml) and T stage as predictors of metastatic disease on bone scans.</p> <p>Choosing a cut point of 10ng/ml gave a positive predictive value of 27.5% (95% CI: 18.4 to 38.8) and an NPV of 100% (95% CI: 90.8% to 100%). Choosing a cut point of 20ng/ml however gave a positive predictive value of 47.5% (95% CI: 36.3 to 58.9) and an NPV of 93.3% (95% CI: 81.8 to 98.4).</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Herranz Amo, 1997. ³⁵ Spain IV	To determine the capacity of PSA, tumour grade and local stage to predict the bone scan findings in patients with newly diagnosed untreated prostate cancer.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 189.</p> <p><i>Patient information</i> Those men with a diagnosis of Prostate cancer made following trans-rectal biopsy and who had no seminal vesicle invasion were studied. Those men with previous treatment or with a previous malignancy were excluded.</p> <p><i>Time period</i> January 1993 to September 1995.</p> <p><i>Methods</i> Patient information was obtained from medical records. PSA was obtained prior to biopsy. Staging was conducted using the TNM system using information from DRE and/or trans-rectal ultrasound.</p> <p>Pathological information was obtained from trans-rectal biopsy and graded according to the Gleason system and stratified for analysis; grade 1 to Gleason 2 to 4, grade 2 – Gleason 5 to 7 and grade 3 – Gleason 8 to 10.</p> <p>Bone scans were taken before treatment was initiated but no information is given on how the bone scans were read. Bone scans were reported as positive, doubtful or negative. Both positive and doubtful scans were categorised as being suggestive of malignancy.</p> <p><i>Statistical methods</i> χ^2 with Yates's correction, Mann Whitney U Test and diagnostic indices.</p>	<p>Of 189 patients, 149 (79%) had negative bone scans. 37 (20%) had positive bone scans and 3 (2%) had doubtful bone scans.</p> <p>The mean PSA level of those patients with a bone scan suggestive of malignancy was $609 \pm 1,009$ng/ml (range 7 to 4,200). This was higher than the mean PSA level of those with negative bone scans (40.8 ± 58ng/ml, $p < 0.001$).</p> <p>One patient had a PSA level below 4ng/ml and was free of metastatic disease. 34 patients had PSA levels between 4 and 10ng/ml and 3 (8.8%) had metastatic bone disease. 44 patients had PSA levels between 10 and 20ng/ml and 1 (2.3%) had metastatic bone disease. 24 patients had PSA levels between 20 and 30ng/ml and 4 (16.7%) had metastatic bone disease. 13 patients had PSA levels between 30 and 40ng/ml and 4 (30.7%) had metastatic bone disease. 73 patients had PSA levels above 40ng/ml and 28 (38.4%) had metastatic bone disease.</p> <p>59 patients had Gleason grade 2 to 4 disease and 9 (15.2%) had metastatic bone disease. 86 patients had Gleason grade 5 to 7 disease and 15 (17.4%) had metastatic bone disease. 44 patients had Gleason grade 8 to 10 disease and 16 (36.4%) had metastatic bone disease.</p> <p>22 patients had Stage T1c disease and 1 (4.5%) had metastatic bone disease. 109 patients had Stage T2 disease and 16 (14.7%) had metastatic bone disease. 56 patients had Stage T3 disease and 23 (41.1%) had metastatic bone disease. 2 patients had Stage T4 disease; neither had metastatic disease.</p> <p>17 of 131 patients (13%) with T1 to 2 disease as compared with 23 of 58 (40%) patients with T3 to 4 disease had metastatic bone disease ($p < 0.001$).</p> <p>53 of 189 (28%) were offered radical treatment; this included 4 patients with metastatic disease demonstrated on their bone scan.</p> <p>Univariate analysis showed that tumour grade ($p = 0.01$), PSA levels ($p < 0.001$) and clinical stage ($p = 0.001$) were associated with metastatic disease on bone scans. Following multivariate analysis, only PSA levels remained significant ($p = 0.0005$). Combining tumour grade and clinical stage with PSA levels did not add to the sensitivity of the PSA alone.</p> <p>The area under the ROC curve was greater for PSA levels than for the stage of disease and the optimal point on the curve was located at 70ng/ml for PSA levels and Stage T2c for clinical stage.</p> <p>Using 10ng/ml as a cut point gave a sensitivity of 92.5%, a specificity of 21.5%, a PPV of 24% and an NPV of 91.5%. Using 70ng/ml as a cut point gave a sensitivity of 65%, a specificity of 82%, a PPV of 57% and an NPV of 90%.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Lee, 2000. ⁴⁵ USA IV	To identify patient characteristics which would identify men in whom bone scans could safely be omitted.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 631.</p> <p><i>Patient information</i> Patients who had bone scans carried out and interpreted in the reporting hospital were included in the study. Only patients who were newly diagnosed and who had not received any form of treatment were studied.</p> <p><i>Time period</i> January 1990 to May 1996.</p> <p><i>Methods</i> Hospital records were reviewed.</p> <p>PSA levels were obtained (at a laboratory where the upper limit of normal was 4ng/ml). PSA levels were stratified as 0 to 15ng/ml, 15 to 50ng/ml or 50ng/ml or more.</p> <p>DRE results were expressed in terms of the TNM system (1992 edition). Stage was stratified as T2b or less and T2c or more.</p> <p>Bone scan reports, recording the interpretation of specialist radiologists, were obtained from the notes.</p> <p>The grade of the tumour was expressed using the Gleason system and stratified a grade 2 to 6, grade 7 or grade 8 to 10.</p> <p>41 patients were excluded from the univariate analysis of the clinical stage and 64 patients were excluded from the logistic regression section of the analysis owing to incomplete data.</p> <p>Various cut points were used and the most effective cut points chosen.</p> <p><i>Statistical methods</i> Multivariate logistic regression, χ^2.</p>	<p>88 of 631 patients (14%) had bone scans suggestive of metastatic disease.</p> <p>Compared with the 328 patients (52.0%) with a PSA level between 0 and 15ng/ml, the 154 patients (24.4%) with PSA levels between 15 and 50ng/ml were to have bone metastases (OR 0.47; 95% CI: 0.28 to 0.78). The 108 patients (17.1%) with PSA levels in excess of 50ng/ml were most likely to have metastatic bone disease (OR 5.25; 95% CI: 3.43 to 8.04) ($p < 0.001$ on univariate regression, $p < 0.001$ on multiple regression).</p> <p>Compared with the 273 patients (43.4%) with Gleason grade 2 to 6, the 188 patients (29.8%) with Gleason grade 7 were more likely to have bone metastases (OR 1.02; 95% CI: 0.62 to 1.67). The 170 patients (26.9%) with Gleason grade of 8 to 10 were most likely to have metastatic bone disease (OR 2.25; 95% CI: 1.43 to 3.54) ($p < 0.001$ on univariate regression, $p < 0.002$ on multiple regression).</p> <p>Compared with the 429 patients (67.9%) with T1a to T2b, the 161 patients (25.5%) with T2c to T4 were more likely to have bone metastases (OR 2.15; 95% CI: 1.54 to 2.99) ($p < 0.001$ on univariate regression, $p < 0.001$ on multiple regression).</p> <p>All 237 patients with Gleason grade 2 to 7, PSA of 15 or lower and a clinical stage of T2b or lower had a negative bone scan. 3 of 71 patients (4.2%) with Gleason grade 2 to 7 and Clinical Stage T2b or lower but a PSA level of between 15 and 50ng/ml had metastatic bone disease diagnosed on bone scanning.</p> <p>Of patients with a PSA in excess of 50ng/ml, 49 of 99 (49.5%) had a bone scan suggestive of metastatic bone disease.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> Pass</p>

Study Country Grade	Aims	Methods	Results	Comments
Lin, 1999. ⁴³ USA IV	To evaluate the role of bone scans in managing newly diagnosed, untreated prostate cancer.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 270.</p> <p><i>Patient information</i> Newly diagnosed patients were studied. All patients were referred for a bone scan. Only patients with histological confirmation were included. Those without PSA levels were excluded.</p> <p><i>Time period</i> January 1995 to October 1997.</p> <p><i>Methods</i> The bone scans were retrospectively evaluated by two nuclear medicine physicians, at the time of imaging and who graded them as positive, negative or indeterminate. Indeterminate cases were referred for appropriate imaging techniques.</p> <p>PSA levels were recorded within 2 months of the biopsy and within 3 months of the bone scan.</p> <p><i>Statistical methods</i> Student's t test. χ^2 test.</p>	<p>270 bone scans were conducted. 24 bone scans (10%) were suggestive of metastatic bone disease and 246 bone scans (90%) graded as normal.</p> <p>249 patients had sextant core biopsy and 21 patients had trans urethral resection of the prostate.</p> <p>The PSA level, the Gleason grade, the T stage of the tumour and the number of cores positive for disease were all correlated with the likelihood of having metastatic bone disease ($p < 0.00001$ in each case).</p> <p>Extent of disease on the bone scan correlated with the PSA level ($R = 0.852$). Patients with metastatic bone disease had a higher PSA level (389 ± 625, median 83.5ng/ml) than those who were free of metastatic disease (14 ± 23.3, median 7.2ng/ml) ($p < 0.0001$).</p> <p>Of the 177 patients with PSA levels below 10ng/ml, three (1.7%) had metastatic bone deposits and all were asymptomatic. 21 of 93 patients (22.6%) whose PSA levels exceeded 10ng/ml had metastatic disease ($p > 0.0001$).</p> <p>Of the 135 patients with one or two positive cores on biopsy, one man (0.7%) had metastatic bone disease. 20 of 114 patients (17.5%) with three or more positive cores had metastatic disease ($p > 0.0001$) (patients who underwent TURP were excluded from this comparison).</p> <p>Of the 131 patients with disease found in one prostatic lobe, only one man (0.8%) had metastatic bone disease. 20 of 118 patients (16.9%) with disease found in both lobes of the prostate had metastatic disease ($p > 0.0001$) (patients who underwent TURP were excluded from this comparison).</p> <p>Of the 160 patients with a Gleason grade of 6 or less, 4 patients (2.5%) had metastatic bone disease. 20 of 110 patients (18.2%) with three or more positive cores had metastatic disease ($p > 0.0001$).</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Lobo, 1999. ³² Chile IV	To assess the usefulness of bone scans in patients with prostate cancer.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 79.</p> <p><i>Patient information</i> Only patients for whom histological confirmation was obtained by biopsy were included.</p> <p><i>Time period</i> January 1995 to June 1997.</p> <p><i>Methods</i> Information was obtained from the medical records and death certificates.</p> <p>Bone scans were classified as positive, indeterminate or negative, but information on who assessed the scans is not reported.</p> <p>The intensity of radiopharmaceutical uptake was graded as follows; 1 = Uptake similar to that of the sacro iliac joints, 2 = Moderate uptake and 3 = Uptake similar to that of the normal bladder.</p> <p>Comparisons were conducted of bone scan appearance with a) levels of bone pain, b) levels of PSA and c) a combination of pain and PSA levels.</p> <p>Patients were stratified according to PSA value (at 4, 10, 50, 100 and 150ng/ml) and according to Gleason score (at Gleason grades 4, 5, 6, 7 and 8.).</p> <p><i>Statistical methods</i> McNemar's test, correlation tests.</p>	<p>22 of 79 patients (28%) had bone scans which indicated the presence of malignant disease. Of the 22 patients with skeletal deposits, 86% had pelvic bone metastases, 67% had rib metastases, 57% had metastases to the vertebrae, 43% had metastases to the bones of the extremities and 24% had metastases to the cranium.</p> <p>Most lesions were of grade 3 intensity. Lesions which were of grade 2 or 3 intensity were significantly more painful than those which were recorded as grade 1 intensity ($p = 0.03$).</p> <p>27 patients reported bone pain (34%). Only 16 of 27 patients (59.3%) had evidence of metastatic deposits on their scans and the location of the pain and of the deposits were frequently different in those who did have both pain and disease on the bone scan.</p> <p>Those patients whose deposits did not cause them pain had fewer metastases than those patients reporting bone pain (5.5 per patient without pain, $n = 11$, as opposed to 27.5 per patient, $n = 11$ with pain, $p = 0.004$). All patients with 20 or more metastases presented with bone pain. No patient with painless bony metastases had fewer than 20 deposits. The sensitivity of pain as a predictor of bone scan results was 50%, the specificity was 72%, the positive predictive value was 40.7% and the NPV was 78.8%.</p> <p>The greatest accuracy in determining which patients had metastases using the PSA assay was achieved by setting the cut point at 50ng/ml. This yielded a sensitivity of 72% and a specificity of 86%. No patient with metastatic disease would have been missed if a cut point of 10ng/ml had been used (NPV = 100%, sensitivity = 100%). However, the PPV (41%) and the specificity (33%) were low at this cut point.</p> <p>The mean PSA values of those men with metastatic disease was higher (347.4ng/ml) than in those men without metastatic disease (32.9ng/ml).</p> <p>A high level of agreement was found between the bone scan and a combination of the PSA levels and the presence of pain.</p> <p>In those patients with metastatic disease, there was positive correlation between the PSA value and the number of metastatic deposits imaged on the bone scan ($r = 0.616$, $p = 0.008$). There was also a significant association between raised PSA levels and the presence (mean PSA = 573.5ng/ml) or absence (mean PSA level = 121.4ng/ml) of pain ($p = 0.022$).</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> Pass</p>

Study Country Grade	Aims	Methods	Results	Comments
Lopez, 1996. ³⁶ Argentina IV	To analyse the correlation between PSA values and bony symptoms and total body bone scans in order to determine the utility of the later technique in patients with adenocarcinoma of the prostate.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 129.</p> <p><i>Patient information</i> A series of 191 patients. Men with no prior therapy and with a PSA level measured before treatment were included in the study. Patients who had had surgical or hormonal manipulation were excluded.</p> <p><i>Time period</i> March 1988 to June 1994.</p> <p><i>Methods</i> No information is given on by whom or how the bone scans were read.</p> <p>All patients had a punch biopsy with subsequent histological confirmation.</p> <p>The methodology used in the determination of the PSA was variable.</p> <p><i>Statistical methods</i> Fischer's exact t test.</p>	<p>PSA values ranged from 1.5ng/ml to 3,750ng/ml with a mean value of 98.95ng/ml \pm 349ng/ml and a median value of 39ng/ml (95% CI: 37.91ng/ml to 160ng/ml).</p> <p>32 of 128 patients (25%) had PSA values below 20ng/ml, 48 patients (37.5%) had PSA values between 20 and 50ng/ml and 48 patients (37.5%) had PSA levels above 50ng/ml.</p> <p>29 patients (22.7%) reported symptoms attributable to metastatic bone disease.</p> <p>57 patients (44.5%) had bone scans which were diagnostic of metastatic deposits.</p> <p>Of the 32 patients with PSA levels below 20ng/ml, 1 patient (3%) had a bone scan suggestive of metastatic bone disease. Of the 48 patients with PSA levels between 20 and 50ng/ml, 22 patient (45.8%) had bone scans suggestive of metastatic bone disease. Of the remaining 48 patients, 34 (70.8%) had positive bone scans.</p> <p>Of the 29 patients who reported symptoms attributable to bone metastases, 28 (96.6%) had positive bone scans. 29 patients of 99 who did not report bone symptoms had bone scans suggestive of metastases.</p> <p>All 30 patients with PSA levels below 20ng/ml and no bone pain were found to be free of metastases on bone scanning. All patients with PSA levels above 20ng/ml and who had bone pain were found to have metastatic disease on their bone scans. The only patient who had a PSA level below 20ng/ml and who had bone pain was found to have metastatic disease on his bone scan.</p> <p>These differences reached statistically significant levels on Fischer's exact t test.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
<p>Maeda, 1997.²⁸ Japan IV</p>	<p>To assess various markers in the treatment of patients with cancer of the prostate.</p>	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 70.</p> <p><i>Patient information</i> Newly diagnosed and previously treated men were included. Hyperparathyroidism, renal failure, gastrectomy and recent history of fracture were all exclusion criteria.</p> <p><i>Time period</i> October 1994 to November 1995.</p> <p><i>Methods</i> Men with histologically confirmed prostate cancer were referred for bone scans. Bone scans were graded according to a 1 to 4 scheme. The grading was carried out by a nuclear medicine physician and a urologist with disagreements resolved by discussion. The extent of the disease was staged using the Whitmore-Jewitt staging system. Biochemical analysis included measurement of PSA, Osteocalcin, Deoxypyridinoline (DPD), Alkaline phosphatase (AlkP), Bone related alkaline phosphatase (BAP) and Pyridinoline cross-linked carboxyterminal telopeptide (I CTP).</p> <p><i>Statistical methods</i> Mann Whitney U Test, Spearmann's Rank Correlation Coefficient and Linear Correlation Coefficient.</p>	<p>38 from 70 patients (54.3%) had bone scans indicative of bone metastases. Of these 24 had previous therapy and 14 patients were newly diagnosed.</p> <p>32 patients had normal bone scans; 2 were newly diagnosed and 30 were patients on systemic therapy.</p> <p>12 patients had repeat bone scans and one of these patients had three bone scans. There were therefore 83 bone scans.</p> <p>All markers were increased in patients with bone metastases with the exception of osteocalcin.</p> <p>Using PSA data, setting a cut point of 4ng/ml yielded a sensitivity of 64.4% and a specificity of 68.4%.</p> <p>Setting a cut point of 10ng/ml yielded a sensitivity of 53.3% and a specificity of 76.3%.</p> <p>Setting a cut point of 20ng/ml yielded a sensitivity of 33.3% and a specificity of 89.5%.</p> <p>Setting a cut point of 50ng/ml yielded a sensitivity of 17.8% and a specificity of 97.5%.</p> <p>No marker was significantly raised in patients with level 1 diseases. Thereafter, an increased level of disease saw increased biochemical markers. I CTP showed the strongest correlation with the extent of the disease (R = 0.649, p < 0.0001).</p> <p>In seven patients with repeated measurement of I CTP, three patients had stable levels and controlled disease. In the remaining four patients, the I CTP levels showed an increase in accordance with disease progression.</p> <p>I CTP had a sensitivity of 48.9% and a specificity of 89.5% when a cut point of 4.9ng/ml was used. The corresponding figures for DPD of 46.7% and 97.4% respectively (cut point = 7.3mol per mol creatinine). The sensitivity for AlkP was 42.2% and the specificity was 100% (cut point = 270 IU/l at 37°C). BAP had a sensitivity of 54.5% and a specificity of 97.4% (cut point 30 U/l at 37°C).</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> No</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Morote, 1992. ⁴¹ Spain IV	To review the clinical information of patients so as to evaluate the possible change in practice.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 144.</p> <p><i>Patient information</i> Patients with prostate cancer and who have received no prior therapy were included in this study.</p> <p><i>Time period</i> Not stated.</p> <p><i>Methods</i> All patients had DRE and, bone scans and the measurements of PSA levels. Diagnostic indices were calculated for PSA cut points of 10ng/ml, 20ng/ml, 50ng/ml and 100ng/ml. No information was given on how or by whom the bone scans were read.</p> <p><i>Statistical methods</i> Diagnostic indices, logistic regression, Mann Whitney U-Test.</p>	<p>83 patients (57.6%) had metastatic disease demonstrated by their bone scans. The remaining 61 patients (42.4%) presented with organ confined or locally advanced disease.</p> <p>Patients with a positive bone scan tended to have higher PSA levels (434.1ng/ml \pm 291.2ng/ml) than those without metastatic deposits on their bone scans (84.9ng/ml \pm 132.1ng/ml) and this difference was statistically significant ($p < 0.001$).</p> <p>Of 10 patients who had PSA levels below 4ng/ml, one man (10%) had metastatic bone disease. Of 6 patients with PSA levels between 4 and 10ng/ml, 1 man (16.7%) had metastatic bone disease. Of 11 patients with PSA levels between 10 and 20ng/ml, 5 men (45.5%) had metastatic bone disease. Of 31 patients with PSA levels between 20 and 50ng/ml, 12 men (38.7%) had metastatic bone disease. Of 19 patients with PSA levels between 50 and 100ng/ml, 10 men (52.6%) had metastatic bone disease. Of 67 patients with PSA levels above 100ng/ml, 54 men (80.6%) had metastatic bone disease.</p> <p>Setting a cut point of 10ng/ml yielded a sensitivity of 97.6%, a specificity of 22.9%, a PPV of 63.2% and an NPV of 87.1%.</p> <p>Setting a cut point of 20ng/ml yielded a sensitivity of 91.6%, a specificity of 32.7%, a PPV of 64.9% and an NPV of 73.9%.</p> <p>Setting a cut point of 50ng/ml yielded a sensitivity of 77.1%, a specificity of 63.9%, a PPV of 74.4% and an NPV of 67.3%.</p> <p>Setting a cut point of 100ng/ml yielded a sensitivity of 65.0%, a specificity of 78.6%, a PPV of 80.5% and an NPV of 62.3%.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments															
Oesterling, 1993. ¹² USA IV	To assess the need for obtaining radionuclide bone scans in the staging of patients with newly diagnosed untreated prostate cancer.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 852.</p> <p><i>Patient information</i> Men, with newly diagnosed cancer of the prostate, with PSA levels of 20ng/ml or less were included. Patients who had undergone treatment of their disease were excluded.</p> <p><i>Time period</i> January 1989 to December 1990.</p> <p><i>Methods</i> A retrospective review of medical notes was conducted. Bone scans were read by nuclear medicine radiologists who were unaware of the PSA levels of the patient and classified as positive, indeterminate or negative. PSA tests were conducted with an assay where the upper limit of normal was 4ng/ml. PSA testing and bone scanning were conducted within 31 days of each other and without intervening procedures. The Mayo Clinic system was used to grade and stage the tumours.</p> <p><i>Statistical methods</i> ROC curves, rates of false negatives and multivariate logistic regression analysis.</p>	<p>852 of 2,064 (41.3%) who were treated for prostate cancer at the reporting hospital had PSA levels of 20ng/ml or less.</p> <p>195 of 852 patients (23%) had normal PSA levels. 366 patients (43%) had a PSA level of 4.1 to 10ng/ml. 175 patients (20%) had a PSA level of 10.1 to 15ng/ml. 116 patients (14%) had a PSA level between 15.1 and 20ng/ml.</p> <p>70 of 852 patients (8%) had Mayo grade 1 disease and none of these men had metastatic disease. 531 patients (62%) had Mayo grade 2 disease and one man (0.2%) had metastatic disease. 220 patients (26%) had Mayo grade 3 disease and 4 (1.8%) of these men had metastatic disease. 31 patients (4%) had Mayo grade 4 disease and 2 (6.5%) of these had metastatic disease.</p> <p>54 of 852 patients (6%) had a Stage A1 tumour; none of these men had metastatic disease. 43 patients (5%) had a Stage A2 tumour and one man (2.3%) had metastatic disease. 36 patients (4%) had a Stage B0 tumour; one man in this group was diagnosed with metastatic disease. 166 patients (20%) had a Stage B1 tumour. 435 patients (51%) had a Stage B2 tumour. 118 patients (14%) had a Stage C tumour.</p> <p>The PSA value was the best predictor of the result of the bone scan. The area under the ROC for PSA was 0.951. The accuracy of the PSA level was not increased by its combination with tumour stage and/or grade.</p> <p>All patients with PSA values in the normal range had normal bone scans. 3 of 366 patients (0.8%) of those with PSA results between 4.1 and 10ng/ml had abnormal bone scans and 1 patient had an indeterminate result. 1 patient of 175 (0.6%) in the group with PSA results from 10.1 to 15ng/ml had an abnormal bone scan. 3 of 116 patients (2.7%) with PSA levels from 15.1 to 20ng/ml had abnormal bone scans and 2 patients had indeterminate results.</p> <p>Of 7 patients with metastatic bone disease demonstrated on their bone scan, 5 reported hip pain and 2 were asymptomatic. PSA levels for these patients ranged from 9.2 to 19.9ng/ml. Additionally, 3 patients (0.3%) had indeterminate bone scans.</p> <p>The observed specificity rates for different PSA cut points are as follows;</p> <table border="0" data-bbox="1238 1324 1901 1500"> <tr> <td>4ng/ml:</td> <td>100%</td> <td>(95% CI: 98.1% to 100%).</td> </tr> <tr> <td>8ng/ml:</td> <td>100%</td> <td>(95% CI: 99.2% to 100%).</td> </tr> <tr> <td>10ng/ml:</td> <td>99.5%</td> <td>(95% CI: 98.4% to 99.9%).</td> </tr> <tr> <td>15ng/ml:</td> <td>99.5%</td> <td>(95% CI: 98.6% to 99.9%).</td> </tr> <tr> <td>20ng/ml:</td> <td>99.2%</td> <td>(95% CI: 98.3% to 99.7%).</td> </tr> </table> <p>The mean charge to the patient was \$602 (USA Dollars, 1993 prices).</p>	4ng/ml:	100%	(95% CI: 98.1% to 100%).	8ng/ml:	100%	(95% CI: 99.2% to 100%).	10ng/ml:	99.5%	(95% CI: 98.4% to 99.9%).	15ng/ml:	99.5%	(95% CI: 98.6% to 99.9%).	20ng/ml:	99.2%	(95% CI: 98.3% to 99.7%).	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>
4ng/ml:	100%	(95% CI: 98.1% to 100%).																	
8ng/ml:	100%	(95% CI: 99.2% to 100%).																	
10ng/ml:	99.5%	(95% CI: 98.4% to 99.9%).																	
15ng/ml:	99.5%	(95% CI: 98.6% to 99.9%).																	
20ng/ml:	99.2%	(95% CI: 98.3% to 99.7%).																	

Study Country Grade	Aims	Methods	Results	Comments
Oommen, 1994. ³⁷ India. IV	To correlate serum PSA levels with bone scans in patients with proven Prostate cancer.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 48.</p> <p><i>Patient information</i> Patients were stratified into three groups; Group 1 included patients with untreated newly diagnosed cancer, Group 2 included patients post local therapy (e.g. surgery or radiotherapy) and Group 3 included patients who had been treated with hormonal therapy.</p> <p><i>Time period</i> June 1991 to October 1992.</p> <p><i>Methods</i> Patients were referred for bone scanning. The images were read by a nuclear medicine physician who had no information regarding to the PSA levels of the patient. PSA levels and bone scans were taken within 2 months of each other. The upper limit of normal on the PSA assay used was 4ng/ml.</p> <p><i>Statistical methods</i> Descriptive statistics.</p>	<p>Of 10 patients in Group 1, the mean PSA was 180.3ng/ml and all patients had PSA above normal. 8 of 10 (80%) had a bone scan suggestive of metastatic disease. All patients in this group had PSA levels elevated above normal.</p> <p>Of 29 patients in Group 2, the mean PSA level was 34.5ng/ml. 18 patients had PSA levels above normal. 10 of 18 (55.6%) had a bone scan suggestive of metastatic disease. Of the remaining 11 patients who had PSA levels below normal, 1 (9.1%) had a bone scan suggestive of metastatic disease.</p> <p>Of 9 patients in Group 3, the mean PSA level was 16.6ng/ml 5 patients had PSA levels above normal. All five patients had a bone scan suggestive of metastatic disease. Of the remaining four patients who had PSA levels below normal, 21 (50%) had a bone scan suggestive of metastatic disease.</p> <p>Of 48 bone scans conducted, 26 (54.2%) were suggestive of metastatic disease. Of these 23 (88.5%) had elevated PSA levels. 2 of 26 (7.7%) were having hormonal therapy for pain. The remaining man (3.8%) represented a false negative for the PSA test.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> N/A</p> <p><i>Inclusion/ exclusion criteria</i> N/A</p> <p><i>Entry point</i> N/A</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> N/A</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Rudoni, 1995. ³³ Italy IV	To evaluate the ability of PSA levels to predict Bone Scan results.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 118.</p> <p><i>Patient information</i> Men with previous treatments were excluded.</p> <p><i>Time period</i> April 1988 to March 1993.</p> <p><i>Methods</i> Bone scans were read by two nuclear medicine physicians who were blinded to the PSA and PAP levels of the patient. Bone scans were categorised as positive, indeterminate (in two cases) or negative. Both indeterminate scans were supplemented by planar imaging techniques and both were subsequently categorised as normal. Case notes were reviewed retrospectively.</p> <p><i>Statistical methods</i> ROC curves.</p>	<p>ROC curves suggest a PSA of 35ng/ml as the optimum cut point for the PSA test. Sensitivity was 83% and specificity was 61%.</p> <p>54 of 118 bone scans (46%) had evidence of metastatic disease.</p> <p>Below 10ng/ml no patients were diagnosed with bone metastases; this cut point had a sensitivity of 100%, a specificity of 36% and an NPV of 100% (95% CI: 86 to 100). Using a cut point of 20ng/ml gave an NPV of 80% (95% CI: 67 to 93).</p> <p>When data from the 73 patients with both PSA and PAP levels were evaluated, the area under the ROC curves was as follows;</p> <p>PSA = 0.93 PAP = 0.81 Grade = 0.61</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> No</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> Pass</p>

Study Country Grade	Aims	Methods	Results	Comments
Ruiz de la Roja, 1995. ³⁸ Spain IV	To evaluate a series of patients to assess the capacity of PSA to predict the existence of bone metastases.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 50.</p> <p><i>Patient information</i> Patients who were not previously treated were included. Patients for whom information on their bone scans or PSA levels were unavailable were excluded.</p> <p><i>Time period</i> January 1992 to December 1993.</p> <p><i>Methods</i> Patients underwent DRE, PSA analysis and bone scanning in all cases. Trans rectal ultrasound (TRUS) was conducted in the cases of 23 patients and Computed Tomography (CT) in the cases of 22.</p> <p>The 1992 edition of the TNM system was used to define the local staging of the prostatic disease. Bone scans were evaluated using Soloway's classification. PSA analysis was conducted in a laboratory where the normal range was 0 to 4ng/ml.</p> <p>Case notes were reviewed retrospectively.</p> <p><i>Statistical methods</i> Diagnostic indices.</p>	<p>20 of 50 patients (40%) presented with metastatic disease on their bone scans. 19 patients (38%) had objectively positive bone scans and one patient (2%) was indeterminate and was analysed with the positive patients. 30 patients (60%) had no evidence of metastatic disease.</p> <p>19 patients (39%) had well differentiated tumours, 19 patients (39%) had moderately differentiated tumours and 11 patients (22%) had poorly differentiated tumours.</p> <p>7 patients had T1 staged tumour and these patients had an mean PSA level of 7ng/ml. 11 patients had T2 staged tumour and these patients had an mean PSA level of 11ng/ml. 23 patients had T3 staged tumour and these patients had an mean PSA level of 23ng/ml. 9 patients had T4 staged tumour and these patients had an mean PSA level of 9ng/ml.</p> <p>Setting a cut point of 10ng/ml yielded a sensitivity of 100%, a specificity of 30%, a PPV of 48% and an NPV of 100%.</p> <p>Setting a cut point of 20ng/ml yielded a sensitivity of 90%, a specificity of 43%, a PPV of 51% and an NPV of 86%.</p> <p>Setting a cut point of 30ng/ml yielded a sensitivity of 90%, a specificity of 60%, a PPV of 60% and an NPV of 90%.</p> <p>Setting a cut point of 40ng/ml yielded a sensitivity of 90%, a specificity of 66%, a PPV of 64% and an NPV of 90.9%.</p> <p>Setting a cut point of 50ng/ml yielded a sensitivity of 90%, a specificity of 73%, a PPV of 69% and an NPV of 91%.</p> <p>Setting a cut point of 60ng/ml yielded a sensitivity of 90%, a specificity of 76%, a PPV of 72% and an NPV of 92%.</p> <p>Setting a cut point of 70ng/ml yielded a sensitivity of 90%, a specificity of 80%, a PPV of 75% and an NPV of 92.3%.</p> <p>Setting a cut point of 80ng/ml yielded a sensitivity of 90%, a specificity of 80%, a PPV of 81% and an NPV of 92.8%.</p> <p>Setting a cut point of 90ng/ml yielded a sensitivity of 90%, a specificity of 90%, a PPV of 85% and an NPV of 93.1%.</p> <p>Setting a cut point of 100ng/ml yielded a sensitivity of 90%, a specificity of 90%, a PPV of 85% and an NPV of 93.1%.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Tekgul, 1995. ³⁹ Turkey IV	To investigate the agreement in findings of bone scans with the serum acid phosphatase (SAP) and the clinical performance scale.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 21.</p> <p><i>Patient information</i> Men were studied in this series if they had histologically proven cancer of the prostate and had metastatic disease.</p> <p>The unit of analysis in this study was a follow-up appointment and not a patient. As such, as some patients were scanned more than once, they contribute more than one set of data to the final results.</p> <p><i>Time period</i> Not stated.</p> <p><i>Methods</i> No information on how bone scans were conducted or read is given.</p> <p>Bone scans and serum acid phosphatase (SAP) were obtained within three months of each other.</p> <p>Each patient was scanned and SAP levels obtained at each clinic appointment. Each patient was assessed by his physician using the Karnofsky scale.</p> <p><i>Statistical methods</i> Descriptive statistics.</p>	<p>Of 29 consultations where progressive disease was diagnosed on the bone scan, the SAP was raised in 20 patients (69%) and normal in 9 patients (31%).</p> <p>Of 8 consultations where non-specific progression was diagnosed on the bone scan, the SAP was raised 1 patients (12.5%) and was normal in 7 patients (87.5%).</p> <p>Of 121 consultations where the bone scan was normal, 12 patients (10%) had raised SAP levels and 109 patients (90%) had normal SAP levels.</p> <p>Of 11 consultations where regression was diagnosed on the bone scan, one man (9%) was found to have raised SAP levels. The remaining 10 patients had normal SAP levels.</p> <p>Of 29 consultations where progressive disease was diagnosed on the bone scan, 15 patients (52%) were clinically evaluation by the patient's clinician as progressing while 14 patients (48%) had normal clinical evaluations.</p> <p>Of 121 consultations with patients who had a normal bone scan, a normal clinical evaluation were found in 111 patients (92%) while 10 patients (8%) were evaluated as clinically deteriorating.</p> <p>Agreement between the bone scans and the SAP was found in the cases of 147/169 consultations (86.9%). Agreement between the clinical evaluation and the bone scan was found in 145/169 cases (85.7%).</p> <p>Of 20 consultations where patients showed elevated SAP levels, all patients still had elevated SAP at their following clinic appointment.</p> <p>Of 15 consultations where patients showed a deteriorated clinical evaluation, the clinical condition of 13 of the patients had not improved by their following clinic appointment.</p> <p>Of 29 consultations where patients showed progression on bone scanning, 9 (31%) had neither clinical deterioration nor raised SAP levels. 4/9 patients showed the metastatic deposits on subsequent bone scanning and showed raised SAP levels and/or clinical deterioration. 5/9 patients showed no signs or symptoms of bone metastases following their bone scan.</p> <p>Of 8 consultations where patients with non-specific disease progression was diagnosed, one patient developed localisable progression.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> N/A</p> <p><i>Inclusion/ exclusion criteria</i> N/A</p> <p><i>Entry point</i> N/A</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> N/A</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Vijayakumar, 1994. ³¹ USA IV	To assess if PSA levels can predict the likelihood that bone metastases will be diagnosed by bone scan in patients with cancer of the prostate.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 90.</p> <p><i>Patient information</i> Men with prostate cancer were included. Those who did not have both a PSA test and a bone scan and those for whom grading and staging information is unavailable were excluded.</p> <p><i>Time period</i> January 1989 to December 1991.</p> <p><i>Methods</i> Whole body bone scans were obtained with local images produced as required. The images were viewed by two nuclear medicine physicians independently and other radiographic techniques were conducted if required; each physician was unaware of additional clinical information.</p> <p><i>Statistical methods</i> Fischer's exact test.</p>	<p>Of 90 patients in total, 62 (69%) had information available on tumour grade. 59 (66%) had information available on the clinical stage of disease. 17 patients had metastatic deposits identified by bone scanning.</p> <p>Of those whose clinical stage was recorded, this stage was unaltered after the bone scan in the cases of 56 patients (95%) and the stage found to be higher than the clinical suspicion in the cases of the remaining 3 men (5%).</p> <p>Of nine patients with clinical Stage A, none were shown to have metastatic deposits on their bone scan. Of 38 patients with clinical Stage B, two men (5%) were shown to have metastatic disease and of twelve patients with clinical Stage C, 1 man (8%) was shown to have a metastatic deposit. This trend for increasing prevalence of metastatic disease with increased clinical stage did not reach statistical significance ($p = 0.688$).</p> <p>Of 19 patients with grade 1 disease, none were shown to have metastatic deposits on their bone scan. Of 27 patients with grade 2 disease, two men (7%) were shown to have metastatic disease and of 16 patients with grade 3 disease, 4 men (25%) was shown to have metastatic deposits. The increasing prevalence of metastatic disease with less differentiated disease was statistically significant ($p = 0.039$).</p> <p>Of 27 patients with PSA levels below 10ng/ml, none were shown to have metastatic deposits on their bone scan. Of 14 patients with a PSA level between 11 and 20ng/ml, one man (7%) was shown to have metastatic disease. Of 31 patients with PSA levels between 21 and 100ng/ml, 6 men (19%) were shown to have a metastatic deposit. Of 18 patients with PSA levels above 100ng/ml, 10 men (56%) were shown to have a metastatic disease. The increasing prevalence of metastatic disease with higher PSA levels was highly statistically significant ($p < 0.001$).</p> <p>The NPVs of the PSA test using varying cut points are as follows:- 10ng/ml: 100%. 15ng/ml: 100%. 20ng/ml: 97.5%. 30ng/ml: 96%. 50ng/ml: 94%</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Pass</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Yolas, 1998. ³⁴ Turkey IV	To identify the relationship between bone scans and other diagnostic methods in detecting bone metastases to identify the conditions necessitating bone scans.	<p><i>Diagnosis</i> Prostate cancer.</p> <p><i>Number of patients</i> 40.</p> <p><i>Patient information</i> 64 patients were diagnosed during the study period.</p> <p><i>Time period</i> October 1993 to May 1996.</p> <p><i>Methods</i> Clinical information was obtained from the notes of patients. Total acid phosphatase levels, prostate acid phosphatase levels, alkaline phosphatase levels and prostate specific antigen levels were recorded.</p> <p>Various imaging techniques including bone scanning, CT, intravenous urography, plain film chest and bone radiographs and ultrasound were conducted to assess the stage of the disease. Patients were staged using the Whitmore-Jewitt staging system.</p> <p>No information on how or by whom the bone scans were read is given.</p> <p>Case notes were reviewed retrospectively.</p> <p><i>Statistical methods</i> Mann Whitney U tests, χ^2 tests.</p>	<p>23 of 40 men (57.5%) had metastatic disease identified on their bone scans.</p> <p>Alkaline phosphatase raised above normal levels had a significant relation with metastatic deposits on bone scans ($p < 0.001$), a sensitivity of 65.2% and a specificity of 88.2%.</p> <p>Total acid phosphatase raised above normal levels had a significant relation with metastatic deposits on bone scans ($p < 0.05$), a sensitivity of 43.5% and a specificity of 88.2%.</p> <p>Prostatic acid phosphatase raised above normal levels showed a trend towards a significant relation with metastatic deposits on bone scans ($p > 0.05$), a sensitivity of 39.0% and a specificity of 76.5%.</p> <p>PSA raised above normal levels had a significant relation with metastatic deposits on bone scans ($p < 0.01$), a sensitivity of 100% and a specificity of 29.4%.</p> <p>No man with a PSA level below 20ng/ml was diagnosed with bone metastases. 5 of 9 patients (55.6%) having a PSA level between 20 and 50ng/ml had bone metastases on their bone scan. 12 of 16 patients (75%) having a PSA level between 50 and 100ng/ml had bone metastases on their bone scan. 6 of 7 patients (85.7%) with PSA above 100ng/ml were diagnosed with bone metastases. 52.2% of patients with metastatic bone disease had pain. 11.8% of patients with no metastatic bone disease had pain.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Cancer of the testes				
Braga, 2001. ⁴⁶ Brazil IV	To identify the role of bone scanning in cases of testicular tumours, regardless of the grade.	<p><i>Diagnosis</i> Seminoma or NSGCT.</p> <p><i>Number of patients</i> 28.</p> <p><i>Patient information</i> 27 men with seminoma and 1 man with NSGCT. Men with histopathologically proven testicular cancer were included in this series.</p> <p><i>Time period</i> Not stated.</p> <p><i>Methods</i> Bone scans which demonstrated abnormal uptake were supplemented by planar radiography. No information is given on the process of reading the scans.</p> <p><i>Statistical methods</i> Descriptive statistics.</p>	<p>In 75% of patients (21/28) the bone scan was normal.</p> <p>The remaining 25% of patients (7 of 28) had variable diffuse uptake of the ipsilateral ilium. Of these seven patients two showed moderate increased uptake of the radiopharmaceutical and subsequent planar radiography was normal. Five patients had significantly increased uptake of the radio-pharmaceutical. Three of these patients had planar radiography reported to be normal while two had abnormalities identified on plain films.</p> <p>Three patients underwent bone biopsy but it is unclear to which of the above groups these patients belong.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Study Country Grade	Aims	Methods	Results	Comments
Cancer of the bladder				
Braendengen, 1996. ⁴⁷ Norway IV	To evaluate the clinical significance of bone scans in patients with clinical stage of T1 to 2 Bladder cancer	<p><i>Diagnosis</i> Bladder cancer.</p> <p><i>Number of patients</i> 121.</p> <p><i>Patient information</i> Analysis was conducted on two samples Groups 1 and 2.</p> <p>Group 1 were those who had radical cystectomy and a preoperative bone scan in 1980 to 1990 (n = 91).</p> <p>Group 2 were those who had a bone scan for muscle invasive cancer in 1988 to 1990 (n = 54).</p> <p>Those from Group 2 who proceeded to have cystectomy were included in Group 1. Those who did not have both a bone scan and a serum AlkP level and those for whom information on grade and stage of disease were unavailable were excluded from the study.</p> <p><i>Time period</i> 1980 to 1990.</p> <p><i>Methods</i> All scans were evaluated by a nuclear medicine physician using a nuclear medicine code (NMC) prospectively:</p> <p>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.</p> <p>These gradings were not added to the patients' records and were not seen by the clinicians involved in the care of the patient.</p>	<p>The NMC and CC were in agreement in 46 of 91 patients (50.5%). 44 of 91 patients (48.4%) were under diagnosed by the clinician and one patient (1.1%) was over diagnosed by the clinician compared with the nuclear medicine physician.</p> <p>From group 1, 14 patients whose nuclear medicine coding indicated bone metastases were offered surgery by their clinician who did not diagnose the metastatic deposits on the bone scan. However, one patient whose NMC indicated disease was confined to his prostate was excluded from surgery owing to the clinician's diagnosis of a metastasis on the bone scan.</p> <p>Elevated alkaline phosphatase was noticed in 5 of 91 patients (5.5%). 3 developed metastatic deposits while 2 did not.</p> <p>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).</p> <p>The NMC classification was a more reliable predictor of extra-osseous disease than the clinician's coding.</p> <p>From group 2, of the 54 bone scans conducted for muscle invasive bladder cancer during the last two years of the study, 51 patients were diagnosed as having no bone metastases and so were referred for cystectomy. Of the remaining three patients who were diagnosed with having metastatic bone deposits, 2 had clinical signs and symptoms suggestive of bone disease. The remaining patient was followed for more than five years and remained free of the signs or symptoms of metastatic bone disease.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> Pass</p>

Study Country Grade	Aims	Methods	Results	Comments
		<p>Scans were instead viewed by the patient's clinician and graded according to the following Clinical Code (CC):</p> <p>I = No pathology. II = Increase uptake, not caused by malignancy. III = Increase uptake suspicious of malignancy. IV = Pathological uptake, most probably owing to metastases.</p> <p>If the oncologist graded the scan as being suspicious of malignancy, a radical cystectomy was not performed.</p> <p>Follow-up was every 3 to 6 months for 5 years and every 12 months thereafter.</p> <p><i>Statistical methods</i> Kaplain Meier survival analysis and Log Rank testing.</p>		

Study Country Grade	Aims	Methods	Results	Comments
Cancer of the kidneys				
Staudenherz, 1998, ⁴⁸ Austria IV	To investigate the diagnostic performance of bone scans in patients with a high pre-test probability for bone metastases owing to abnormal laboratory tests, pain or confirmed non-osseous metastases.	<p><i>Diagnosis</i> Renal cell cancer.</p> <p><i>Number of patients</i> 36.</p> <p><i>Patient information</i> Only patients with confirmed RCC who had pain, with abnormal biochemical tests and/or confirmed non-bone metastases were included in the study. Included patients were those with disease clinically suspicious of bone metastasis who were referred for a bone scan.</p> <p><i>Time period</i> Not stated.</p> <p><i>Methods</i> Bone scans were read by the two radiologists and disagreements resolved by discussion. Radiologists were blinded to the clinical information of the patient. Laboratory tests were conducted within two weeks of the bone scan. Data were collated retrospectively.</p> <p><i>Statistical methods</i> Logistic regression.</p>	<p>6/36 patients (17%) were suspected of having a bone metastasis owing to severe pain.</p> <p>18/36 patients (50%) had confirmed metastases outside the skeleton.</p> <p>23/36 patients (64%) had abnormal biochemical markers.</p> <p>14/36 (44%) patients had a clinical diagnosis of metastases to bone (11 diagnosed by CT and 3 by open biopsy).</p> <p>1 of 14 patients had a bone scan which was diagnostic of malignancy (sensitivity = 7%, specificity = 100%, accuracy = 64%).</p> <p>In addition to the one patient who had strongly increased uptake, 10 of 14 patients had faintly increased uptake of the radioisotope on their bone scans. Taking this as the diagnostic threshold, the sensitivity was 79%, the specificity was 73% and the overall accuracy was 75%. Three patients with metastatic bone disease were not identified on bone scanning and six patients with no evidence of bone metastases were shown to have increased uptake of the radioisotope.</p> <p>Increased serum alkaline phosphatase was seen in 4 of 14 patients (29%) with metastatic bone disease and in 7 of 22 patients (32%) of those without metastatic bone disease.</p> <p>Logistic regression of patient characteristic failed to identify any diagnostic pattern suggestive of bone metastases.</p>	<p>Grade</p> <p><i>Population</i> Pass</p> <p><i>Reference standard</i> Pass</p> <p><i>Blinding</i> Not stated</p> <p><i>Case control</i> Pass</p> <p>Quality</p> <p><i>Sample</i> Pass</p> <p><i>Inclusion/ exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> N/A</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

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Patient-Centred Care

The Questions

- a) Do psychosocial interventions improve the quality of life or reduce stress in patients with urological cancer?
- b) Do psychosocial interventions increase satisfaction with treatment in patients with urological cancer?
- c) What methods of information-giving have been proposed to improve communication with cancer patients and how effective are they?
- d) What training should health professionals be given to improve communication with cancer patients?
- e) What methods of information giving have been effective in reducing anxiety and helping patients make informed decisions in urological cancer?
- f) What information should urological cancer patients be given at different stages of care?

The Nature of the Research Evidence

a) Psychosocial interventions

Two meta-analyses^{1, 2} (Table 3.1a) and five RCTs³⁻⁷ (Table 3.1b) were identified. One of the trials specifically evaluated psychosocial interventions in testicular cancer.⁶

b) No studies that addressed this question were identified.

c) Information-giving

A systematic review from the Cochrane collaborative that evaluated the effectiveness of different methods of providing information to cancer patients, their families and carers was located⁸ (Table 3.2a). In addition, 17 studies not included in the Cochrane review were located (Table 3.2b); these include six RCTs⁹⁻¹⁴ and ten non-randomised comparison studies or observational studies.¹⁵⁻²⁴

d) Training for health professionals

Ten studies specifically evaluated communication skills training for health professionals²⁵⁻³⁶ (Table 3.3). All the studies were observational and were of a pre/post, repeated measures or longitudinal designs.

e) No studies that addressed this question were identified.

f) No studies that addressed this question were identified.

Summary of the Research Evidence

a) Psychosocial interventions

There is a growing body of evidence indicating the need for psychotherapeutic interventions to assist patients and their families through the cancer experience.³⁷⁻³⁹ The literature highlights that this need may arise at any stage throughout the disease trajectory, from the initial diagnosis through to curative and palliative stages. Psychological morbidity is common in patients with advanced cancer – 37% to 63% of patients show psychological morbidity.⁴⁰⁻⁴²

An eclectic mix of psychotherapeutic interventions has been employed to meet the various needs of different patients and have been categorised in various ways by researchers who have reviewed this topic. An analysis of 62 treatment control comparisons in 45 studies concluded that psychosocial interventions have positive effects on emotional adjustment, functional adjustment and treatment and disease-related symptoms in adult cancer patients.² A meta-analysis of 116 studies concluded that psychoeducational care was found to benefit adults with cancer in relation to anxiety, depression, mood, nausea, vomiting, pain and knowledge levels.¹

‘Psychoeducational care’ covers a plethora of techniques, many of which have been shown to be useful. For example, guided imagery, muscle relaxation, systematic desensitisation and meditation were effective for treating nausea. However, the meta-analysis was unable to assess the relative effectiveness of these various types of psychoeducational care.

All RCTs investigated some form of cognitive behavioural therapy (CBT) and involved comparison of CBT with a control group who received a non-structured supportive therapy and/or a group who received standard care.

Follow-up periods varied between RCTs. A study investigating the value of home support for cancer patients found that anxiety and depression scores in patients that received social support from an oncology nurse were lower than those in the control group, but that these differences were not sustained longer than the intervention period.⁷

Two studies found that beneficial effects of social support or cognitive-behavioural therapy lasted longer than the intervention period:^{4,5} these beneficial effects were seen at six months follow-up in one study⁴ and improvements in a number of psychological symptoms and cognitions relating to diagnosis and prognosis were evident at one year follow-up in the other.⁵ Both studies investigate the intervention in comparison with both a non-structured intervention and with standard care.^{4,5} Adjuvant psychological therapy (APT), a type of cognitive therapy designed specifically for use in cancer patients, was compared with non-structured therapy. APT resulted in greater and more sustained improvements in patients’ adaptation to cancer in patients’ ability to cope with their disease.⁵ In the other study, whilst both cognitive therapy and social support were found to be effective, social support had longer lasting benefits.⁴

Conclusions

Overall these studies show at least initial good effects of various psychosocial interventions in the care of patients and their families. Variability in the studies is an obstacle to identifying the optimal therapy in terms of type, number of sessions, at what stage in the course of the disease and which patients will respond most positively. Added to this, many of the studies fail to detail precisely the therapies or outcome measures used.

b) No studies that addressed this question were identified.

c) Information-giving

A variety of methods aimed at improving the communication process have been proposed and evaluated. These include:

- Providing an audio-tape of the consultation or a letter summarising the consultation.^{8, 14, 18}
- Providing a written questionnaire completed in the clinic to elicit patients' concerns (replacing the word 'cancer' with 'illness').⁸
- Offering patients information only when they request it and only to an extent that they want. This is supplemented by a written record and/or a tape recording of the consultation.⁸
- Sending an information package before consultation at a tertiary cancer centre.¹³
- Establishing a structured patient-centred group educational programme.⁴³
- Establishing a common system of documentation of information and/or care such as a shared-care record containing appointments, a diary of significant events, medications, carers' addresses and contact numbers.^{12, 19, 24}
- Showing a preparatory slide show to inform patients prior to procedures.²²
- Supplying information and support via telephone help-lines to cancer patients, their family and the general public.^{21, 23}
- Using care packages consisting of several interventions to improve communication, such as written materials, a record sheet of information given, records of interaction with health professionals and mapping of problems.²⁰
- Implementing individualised structured nursing interventions to assess each patient's needs and providing the knowledge and skills needed through home visits to empower the patient.¹⁵
- Publishing general and specific cancer information booklets.^{10, 11, 16}
- Utilising audio-visual and/or written information-based interventions about cancer pain and its management.⁹

Most studies have concluded that patients find audiotapes or written summaries valuable.^{8,9,14,18} Improvements in information recall have been found in some, but not all, studies.⁸

One RCT compared audiotapes and a summary letter and offered patients the choice of these or other information delivery methods. It was found that audiotapes were preferred above a summary letter, a talk with the oncology nurse or a telephone call.⁸

There has been a failure to demonstrate that audiotapes improve levels of anxiety, depression or psychological distress.⁸ A study found that patients who received an audiotape of their consultation could recall more details of what was discussed and were more satisfied with the consultation overall.¹⁴ However, audiotapes may be detrimental to patients with a poor prognosis, distressing to a minority of patients and unsatisfactory to those wanting minimal news.⁸ This suggests that it is necessary to assess patients' informational needs beforehand. Overall, studies in this area are small, heterogeneous and use different outcome measures. As a consequence, cross study comparisons are difficult to accomplish, but it is possible that recordings or summaries may benefit patients with cancer.

The use of information booklets is widespread in cancer education, with limited information on efficacy.¹⁶ The type (general or specific), presentation, comprehension and provision of five commonly used cancer information booklets were investigated in a US study.¹⁶ It was found that patients much preferred booklets written at grade eight English. This is the average educational standard of thirteen year-olds. These were well utilised by patients and their families. Most patients favoured receiving general cancer information at the treatment decision stage to facilitate informed decisions. The degree to which the patient actively sought information did not affect levels of satisfaction, which were high for all five booklets.

Further evidence to support the use of written information as a means of communication comes from two RCTs.^{11,13} Receiving preparatory written information prior to a clinic appointment, whether by mail or at the clinic before the consultation, resulted in patients being better informed and less confused about the reasons for the appointment.¹¹ This was strengthened by a later study where new patient information packages received before the first appointment were useful in meeting the informational needs of patients.¹³ The timing of the provision of information appears to be important in preparing patients for an event.

A study using a slide show to prepare patients for radiotherapy found that the show helped alleviate anxiety and reduce mood disturbance at follow-up.²²

Anticipating needs of patient and relatives can help both to cope with events. A videotape intervention and accompanying booklet helped patients prevent and control pain.⁹ Structured patient-centred interventions with elements of counselling and support either in groups⁴³ or individually¹⁵ were identified as effective means of communication. The importance of information and support was highlighted in a study where a structured nursing intervention was evaluated.¹⁵ Empowering the patient with the relevant knowledge and skills

improved symptom awareness, decreased symptoms and increased perceived support.

Improving information giving to patients and documenting the information given may be of value not only to the patient and their family but also to carers and health professionals. Appropriate interventions may improve the continuity of patient care.^{12,19,20,24}

As a general source of cancer information and support available to patients, family and the general public, telephone information help-lines are a good resource. Evaluative studies indicate that the majority of callers are satisfied with the quality and the amount of information they received.^{21, 23} The amount of callers contacting the service implied that callers have a genuine need for more sources of information.

The studies identified varied in terms of quality. Furthermore, several different outcomes have been used as measures for improved communication. These include symptom management, knowledge, recall, satisfaction, continuity of care, affective states, self-care, patient empowerment, independence, preparedness for events, perceived problems and understanding.

Conclusions

Three main techniques for imparting information to patients have been evaluated: audiotapes, written information and telephone helplines. Whilst these techniques have been in the main well received, at present it is not clear which method is best for improving quality communication between patients, their families and health care professionals.

d) Training for health professionals

Communication skills training evaluated in the studies can be sub-divided into 'micro' and 'macro' skills. Micro-skills – specific behaviours such as non-verbal communication and paralanguage. (Paralanguage refers to how a message is conveyed rather than the linguistic content of the message. For example, head movements, pausing, emphasis and tone, verbal skills, type of questioning and listening skills.) Macro-skills – personal insight into attitudes and feelings about communicating with cancer patients, basic counselling skills to facilitate patient and family assessments and strategies to deal with difficult situations such as giving patients bad news. These build on micro-skills and are the more complex cognitive, emotional and behavioural aspects of communication.

Studies varied in their content and design, but tended to use a combination of didactic and experiential methods. For example, teaching, role play, feedback, group work and discussion were assessed by a number of studies.^{26, 29-32}

Although the programs differed in length and outcomes, the training method improved health professionals' skills in effective interaction³⁰⁻³² and helped instil strategies for giving distressing information.²⁶ Despite these benefits, inhibitory behaviours such as blocking patients' responses were still present in three studies. In two studies follow-up evaluations at six months showed that inhibitory behaviours had reverted to pre-training levels.^{30, 31} An informal evaluation of the reasons why the initial gains dissipated revealed that staff had anxieties about their ability to deal with emotional situations. Training which fails to address participants' concerns may not be effective. In one of the

investigations, however, improvements in communication skills of undergraduate medical students were still present two years after completion of the communication skills course.²⁹

Studies that have explored participants' feelings and attitudes have tended to rely on experiential methods. This approach was assessed while teaching medical students communication with terminally ill cancer patients.²⁵ Students were encouraged to challenge their beliefs and opinions about giving bad news to a patient in a case study. This was achieved by group work with open discussion and modelling of the desired behaviour using a video with the case study acted out. Following the session, an increase was reported in the numbers willing to take responsibility for informing the patient about their diagnosis and/or prognosis. The greatest changes were seen in those who initially stated they would not tell the patient they had cancer. A similar finding was reported using open discussion and role play to examine attitudes.³⁴ Those participants with negative attitudes before the training showed a marked increase in positive attitudes after training.

There are two notable problems with these studies. Firstly, their reliance on self-report as a means of evaluation may have biased the findings. Secondly, a change in attitudes does not always result in behaviour change; the relationship between attitudes and actions is more complex and involves a number of other factors.⁴⁴

Criticism of the studies is justifiable in that the aims of the studies were to translate training into practice to improve patient care. Only three studies have examined the effects of training on clinical practice.^{28, 35, 36} Assessments of hospice nurses' communication skills before and up to nine months after training resulted in improvements in micro-skills. However, there was little change in the nurses' ability to elicit patients' concerns.²⁸

In contrast, an evaluation of a program aimed at nurses' performance of patient assessment showed it to have a positive impact on communication.³⁶ Patient assessments were better structured, covered more areas and improved on psychological aspects after the training. These gains were maintained at nine months. A longitudinal follow-up of a sub-set of nurses at one year post-training showed that these gains were maintained. Moreover, their skills at psychological assessment had improved.³⁵ In contrast to the former study, the latter investigation was more comprehensive and included both micro- and macro-skills training.³⁶ A large component of the training involved experiential learning over an extended period of time. This enabled nurses to put their knowledge into practice and to obtain personal feedback. Nurses were encouraged to critique their own performance, raising their awareness of the importance of communication.

All of the studies reported positive outcomes as a result of the communication skills training. However, the findings need to be viewed with caution owing to the criticisms raised. In addition to this, none had comparison groups; the changes may therefore not be reliably attributed to the training. Having stated this, comparison studies are not easy to perform in this type of research because of potential confounding factors. Studies such as RCTs, despite their methodological rigour, may do little to disentangle specific factors that may have contributed to the improvements.

Conclusions

The evidence suggests that the use of both didactic and experiential methods improve some aspects of communication. Training should also incorporate both micro-skill and macro-skills to equip the health professional with the competency to employ these techniques.

- e) No studies that addressed this question were identified.
- f) No studies that addressed this question were identified.

Table 3.1a Effectiveness of psychosocial interventions on the quality of life of patients with urological cancer: systematic reviews

Study Country Grade	Aims	Patient population	Content of intervention	Outcome
Devine, 1995. ¹ USA III	To perform a meta-analysis and review of psycho-educational programmes aimed at improving the psychological and physical well-being of cancer patients.	<p>116 studies</p> <p>The studies assessed 7 outcomes:- Anxiety; depression; mood; nausea; vomiting; pain; knowledge.</p> <p><i>Sample characteristics</i> Age range 27 to 69. 70% of the studies had more female participants; 18% had only females. The majority (55%) involved various malignancies.</p> <p>Meta-analysis performed on 98 of the 116 studies (n = 5,326 patients).</p>	<p><i>Inclusion criteria</i> Experimental, quasi-experimental and pre/post single group designs with more than five patients in each treatment group. 87% of studies had control groups and 68% of studies randomly allocated them to their groups.</p> <p><i>Interventions</i> 38 cognitive therapies (CT), behavioural therapies (BT) or cognitive behaviour therapies, (CBT) (e.g. muscle relaxation, guided imagery). 19 combinations of CBT with relaxation/non- relaxation interventions (e.g. problem solving). 20 educational interventions (e.g. general cancer information). 20 education with counselling (various types but excluding CBT). 3 BT combined with non-CT or non-CBT.</p>	<p>A large degree of heterogeneity was seen in knowledge levels. An intermediate level of heterogeneity in effect size was seen in other outcome measures.</p> <p>Levels of anxiety were reduced in 95% of studies.</p> <p>Levels of depression were reduced in 92% of studies.</p> <p>Levels of nausea were reduced in 11 of 27 studies which utilised BT models such as systematic desensitisation, meditation, guided imagery or muscle relaxation.</p> <p>Levels of pain were reduced by relaxation strategies such as muscle relaxation, guided imagery or music therapy.</p> <p>Levels of knowledge were increased by education/teaching, especially when written material was included but the effect was heterogeneous across the studies.</p>

Study Country Grade	Aims	Patient population	Content of intervention	Outcome
Meyer, 1995. ² USA III	To perform a meta-analysis of published RCTs of psychosocial interventions with adult cancer patients.	<p>45 studies incorporating 62 treatment to control comparisons with 5 from the UK, 36 from the USA, 2 from Canada and one each from Columbia and Egypt.</p> <p>Studies assessed five categories of dependent measure:-</p> <p>Emotional adjustment; functional adjustment; treatment or disease; related symptoms; medical measures.</p> <p><i>Sample characteristics</i> Where mean age was reported, the values clustered around 50yrs.</p> <p>55% of studies reported gender and had more than 60% female participants.</p> <p>14 from 45 were single location / type of cancer.</p> <p>The total sample size was not given.</p>	<p><i>Inclusion criteria</i> Published RCTs of groups of adult patients with cancer.</p> <p>Patients who received psychosocial, behavioural or psycho-educational interventions.</p> <p>Studies which compared the intervention with another group of cancer patients either receiving no psychosocial intervention or an extremely minimal/placebo procedure.</p> <p>Outcome variables included the patients' behavioural, emotional physiological or medical state.</p> <p><i>Interventions</i> Cognitive-behavioural therapy. Informational and educational treatments. Non-behavioural counselling or psychotherapy interventions. Social support. Other therapy e.g. music therapy. (numbers of each type of study not given)</p>	<p>One study was removed from the analysis as the participants were not aware that they had cancer. Thereafter the effect sizes were homogenous for all five categories of dependent measure.</p> <p><i>Average effect sizes</i> Psychosocial interventions have positive effects on emotional adjustment, functional adjustment and treatment and disease-related symptoms in adult cancer patients. No significant effect was seen for medical outcomes however these studies involved the smallest numbers of subjects.</p> <p>Emotional adjustment: $d = 0.24$ (95% CI: 0.17 to 0.32). Functional adjustment: $d = 0.19$ (95% CI: 0.06 to 0.32). Treatment- and disease-related symptoms: $d = 0.26$ (95% CI: 0.16 to 0.37). Medical: $d = 0.28$ (95% CI: 0.10 to 0.44).</p> <p>Interventions: no difference between intervention type and outcome (by dependent measure).</p> <p><i>Analysis</i> Unbiased estimate of unit free effect size 'd' = The difference between mean outcome scores in treatment and control group multiplied by a correction factor for the small sample size and divided by pooled standard deviation.</p>

Table 3.1b Effectiveness of psychosocial interventions on the quality of life of patients with urological cancer: primary studies

Study Country Grade	Aims	Patient population	Study design and outcome measures	Results
Connor, 1992. ³ USA II	To examine the effects of psychosocial intervention on denial-related coping ability.	24 terminally ill cancer patients with intrapersonal denial, referred by a medical oncologist. 21% male, 79% female. Mean age 61. <i>Types of cancers</i> Not reported	RCT. <i>Intervention</i> Talking openly with the Hospice Director about their illness, its impact on them and their family and their hopes and fears. 13 patients were included in the intervention arm and 11 were included in the control arm. Follow-up was 2 to 3 weeks after the initial interview.	A reduction in denial was seen in the patients in the intervention group. Those in the control group saw an increase in denial.
Evans, 1995. ⁴ USA II	To evaluate the effects of cognitive-behavioural and socially supportive group therapy.	72 depressed Stage II cancer patients about to proceed to external beam radiotherapy at a teaching hospital. 62% male, 38% female. Mean age 54 years. <i>Types of cancers</i> Lung - 42%, Bladder - 30%, Prostate - 22%, Head and neck cancer - 6%.	RCT. All patients' scores on 'Centre for Epidemiological Studies Depression Scale' (CES-D) indicated depression. Patients participated in 8 weekly one hour social worker-led sessions. They were allocated to one of three arms:- Group 1 (n = 29) – Cognitive behavioural treatment by utilising various skills training to reduce anxiety. Group 2 (n = 23) – Social support by encouraging participants to adopt mutually supportive roles in the group. Group 3 (n = 26) – No treatment (other than crisis intervention when required). <i>Assessment</i> At baseline, at eight weeks (post intervention) and at six months post intervention using CES-D Social Provisions Scale the SCL-90-R and the Multi-dimensional Health Locus of Control Scale (MHLC).	Patients in both groups 1 and 2 experienced less depression ($p < 0.01$), hostility and somatisation following therapy than patients in the control group (group 3). At six months follow-up, the social support group participants had less somatisation ($p < 0.01$) less depression ($p < 0.01$) and less anxiety ($p < 0.05$) than control group.

Study Country Grade	Aims	Patient population	Study design and outcome measures	Results
Moorey, 1998. ⁵ UK II	To compare adjuvant psychological therapy (APT) and supportive counselling in patients with cancer.	<p>57 consecutive patients referred for psychiatric assessment to a Psychological Medicine Group who met the criteria for an abnormal adjustment reaction.</p> <p>Mean age 51.</p> <p>16 males, 35 females.</p> <p>Median time since diagnosis - 10 months in the APT group and 14.2 months in the counselling group.</p> <p><i>Types of cancers</i></p> <p>Breast - 40%, Lymphoma - 11%, Prostate - 4%, Other - 45%.</p>	<p>RCT.</p> <p>Therapies included 8 weekly sessions (including spouse where appropriate).</p> <p>An adjuvant psychological therapy (APT) cognitive-behavioural therapy model specifically for cancer patients was used. The therapy teaches coping strategies. This was compared with supportive counselling. This was designed to control for therapist's time and attention but excluded elements from APT.</p> <p><i>Assessment</i></p> <p>Assessment was a baseline, at 8 weeks, at 4 months and at 1 year and consisted of the Hospital Anxiety and Depression Scale (HAD), the Spielberger Trait Anxiety Inventory (STAI), the Beck Depression Inventory (BDI), the Mental Adjustment to Cancer Scale (MACS) and the Cancer Coping Questionnaire.</p>	<p>Change over time:-</p> <p>Patients managed with APT saw a significant change on 9 of 10 variables at 2 months and 4 months and saw a significant change on 7 of 10 variables at 1 year.</p> <p>Patients managed with counselling saw a significant change on 4 of 10 variables (2 months), 6 of 10 variables (4 months) and 5 of 10 variables (1 year).</p> <p>Comparison of therapies.</p> <p>APT greater change from baseline at 2 months than counselling as measured by the HAD scale, 2 MACS sub-scales and the cancer coping questionnaire.</p> <p>Mean self-defined problems persisted at 4 months.</p> <p>Clinical significant comparisons:-</p> <p>100% of patients managed with APT and 82% of those managed with counselling scored more than 8 on the HAD anxiety scale at baseline. This declined to 29% for APT patients and 71% for counselling patients at 4 months.</p> <p>The incidence of depression was halved in APT patients at 2 and 4 months while its incidence declined from 59% to 43% at 4 months in the counselling group.</p>

Study Country Grade	Aims	Patient population	Study design and outcome measures	Results
Moynihan, 1998. ⁶ UK II	To determine the efficacy of adjuvant psychological therapy in patients with testicular cancer.	73 newly diagnosed testicular cancer patients recruited from a tertiary cancer care centre. 40% of eligible patients agreed to participate in the trial. Mean age 61 years. <i>Types of cancer</i> Not reported.	RCT. A cognitive and behavioural treatment (CBT) programme consisting of six 1 hour sessions over 8 weeks was offered to patients in the intervention group. More or fewer sessions were available as necessary. Sessions were conducted by a registered mental health nurse. The patients in the control arm received no intervention above normal care and agreed to complete scales. 31 and 37 patients respectively participated in the control and intervention arms of the study. <i>Assessment</i> Assessment occurred at baseline, at 2, 4 and 12 months and was by means of the Hospital Anxiety and Depression Scale (HAD), Mental Adjustment to Cancer (MAC), Psychosocial Adjustment to Illness Scale, Rotterdam Symptom Checklist (RSCL), emotional concealment sub-scale of the Brannon Masculinity Scale and the Reiker Sexual Adjustment Scale.	No differences between the intervention and control groups were seen during follow-up. 81 patients that were approached about entry into trial but declined psychotherapy agreed to be followed up as per study protocol. These patients were those with early stage disease and fewer physical symptoms than those who agreed to participate in trial.
Barker, 1997. ⁷ UK IV	To investigate whether oncology home support improves psychological morbidity during or after treatment is completed.	58 female patients were recruited from one hospital oncology outpatient department. Group A – n = 36. Mean age 60. Group B – n = 51. Mean age 58. <i>Types of cancers</i> Not reported	A cross-over trial utilising a within-and-between subjects design with patients allocated to groups dependent on an odd or even year of birth. Group A (20 completed). During the first 4 months of therapy, they received usual care during their treatment (consisting of hospital appointments only). During the second 4 months, this was supplemented by weekly visits by an oncology nurse following treatment. Group B (38 completed). During the first 4 months, this was supplemented by weekly visits by an oncology nurse following treatment. During the second 4 months of therapy, they received usual care during their treatment (consisting of hospital appointments only). <i>Assessments</i> All patients were visited at baseline (day 1) and at 2 months. Assessments were performed monthly from baseline with the Hospital Anxiety and Depression Scale (HAD) and Rotterdam Symptom Checklist (RSCL)	Group A – usual care during treatment, supportive care afterwards – 30% were classified as ‘at risk’ (HAD scores > 11) at 4 months. This steadily declined with weekly support but at 8 months this increased sharply to 35%. The RSCL scores showed a similar pattern. Group B – supportive care during treatment, usual care afterwards – during weekly support there was a decline in levels of anxiety from 22% of patients ‘at risk’ at baseline to 5% at 4 months; this increased slightly to 12% at 12 months. Again, a similar trend was seen in RSCL scores. <i>Comparing groups A and B</i> The supportive intervention was more effective during rather than following treatment.

Table 3.2a Methods of providing information to improve communication with cancer patients: systematic review

Study Country Grade	Aims	Study criteria & assessment	Results	Comments
Scott, 2001. ⁸ UK I	To examine the effects of providing recordings or summaries of their consultations to people with cancer and their families.	<p><i>Inclusion criteria</i> Randomised or non-RCTs which evaluate the effects of providing audiotapes or summaries of consultations.</p> <p><i>Data collection and assessments of studies</i> Two reviewers independently assessed the relevance of titles and abstracts.</p> <p><i>Literature searches</i> Each accepted study was assessed for methodological quality based on eight criteria.</p> <p>Three effect types were looked for: information recall/ understanding, experience of health care and health and wellbeing</p>	<p>8 studies satisfied the inclusion criteria.</p> <p><i>Benefits of receiving recordings or summaries</i> In 7 studies 83% to 96% of participants found recordings or summaries of their consultations valuable.</p> <p>4 out of 6 studies reported better recall of information.</p> <p>2 out of 4 studies found that participants were more satisfied with the information received.</p> <p>None of six studies found any effect on anxiety or depression.</p> <p>No study evaluated effect on quality of life or survival.</p>	<p>The studies did not measure similar outcomes.</p> <p>When practitioners are aware they are being recorded, it is possible that there might be a positive impact on the content of consultation.</p> <p>Recording of consultations may also affect patients' consultation behaviour. Participants in control groups were aware that their consultation were not being recorded and this may have affected their responses to the research instruments.</p> <p>Studies were small and heterogeneous. The evidence is not strong, but it is possible that the provision of recordings or summaries may benefit patients with cancer.</p>

Table 3.2b Methods of providing information to improve communication with cancer patients: primary studies

Study Country Grade	Aims	Study details	Outcomes	Results
Clotfelter, 1999. ⁹ USA II	To assess the efficacy of an educational intervention on patient's pain management and pain intensity.	<p><i>Participants</i> 36 elderly cancer patients aged between 66 to 88 years. 36% male, 64% female.</p> <p><i>Types of cancers</i> Lung (n = 3) Bladder (n = 1) Breast (n = 19) Prostate (n = 7) Colon (n = 3) Lymphoma (n = 3)</p> <p><i>Intervention</i> Patients in the intervention group (n = 18 from 36 patients in total) were given a booklet 'Managing Cancer Pain'. Patients and their spouses watched a 14 minute video which discussed communicating pain needs, medication addiction, tolerance and side effects, medication types and administration, support groups and non-drug interventions.</p> <p><i>Design</i> RCT; repeated measures design; patients recruited from one private oncology practice. All participants assessed their present pain intensity at the start of the study and 2 weeks later at 2 different times of the same day.</p>	<p>Visual analogue scale (VAS).</p> <p>Patients marked their present level of pain along a horizontal line from 'no pain' to 'worst pain imaginable'.</p> <p>2 ratings on the same day were used as an average pain intensity rating.</p>	<p><i>Pre-intervention comparisons</i> Patients in the control group had a higher mean level of pain (17.5) than those in the intervention group (14.2). This was controlled for in post-intervention analysis.</p> <p><i>Post-intervention comparisons</i> Patients in the intervention group had significantly lower mean level of average pain intensity (16.3) than patients in the control group (29.4).</p> <p><i>Pre/post intervention pain levels</i> Both the control and intervention groups showed a slight increase in pain over the study period. The average pain intensity was rated mild to moderate.</p>
Eardley, 1988. ¹⁰ UK II	To assess the impact of a booklet about radiotherapy on patients' worries about treatment and satisfaction with information about radiotherapy	<p><i>Participants</i> 415 new patients scheduled for a course of radiotherapy and waiting for treatment at a tertiary referral centre.</p> <p><i>Types of cancers</i> Not reported</p> <p><i>Intervention</i> Patients in the intervention group (n = 200 of 415 in total) were mailed the booklet and questionnaire about worries concerning radiotherapy. Patients in the control group were sent the questionnaire but no information booklet was enclosed.</p> <p><i>Design</i> Patients were allocated to receive or not receive the booklet randomly. No information on blinding was given. A postal questionnaire was sent to all patients.</p>	Ad hoc mail questionnaire	<p>80% patients thought the booklet was a good idea and 66% found it helpful.</p> <p>Patients receiving the booklet were significantly less concerned about side effects and more satisfied with information.</p>

Study Country Grade	Aims	Study details	Outcomes	Results
Huchcroft, 1984. ¹¹ Canada II	To evaluate the efficacy of a general cancer information booklet in preparing patients for their first visit to a cancer centre.	<p><i>Participants</i> 161 cancer patients due to attend a cancer clinic during an 11 month period. Patients were stratified into one of three groups which were comparable in relation to age and sex.</p> <p>Mail group: (n = 32) received a booklet by mail before the visit. Before group: (n = 50) received the booklet at the first visit before interview. Control group: (n = 79) given booklet after interview on the first visit.</p> <p><i>Types of cancers</i> Not reported</p> <p><i>Intervention</i> A booklet which included information about the centre, transportation, care and treatments, resources and services, volunteers, financial matters and a support organisation, the Canadian Cancer Society.</p> <p><i>Design</i> RCT with blind coding of interview schedules. The patients were recruited from the appointments register 10 days prior to their first clinic visit and randomly assigned to one of 3 groups.</p>	Interviewed at the clinic on the first visit using an 18 question pre-coded interview schedule. Open-ended and multiple choice questions which assessed the patients' impression of the visit, knowledge of their disease and treatment, knowledge of resources and helpfulness of the booklet.	<p>Those who received the booklets prior to interview were better informed about specific/non-specific cancer resources. There were no significant differences between the groups given the booklet prior to interview.</p> <p>Patients in the intervention group were more likely to feel well informed and demonstrated higher scores on 4 out of 7 items on the check list.</p> <p>Patients in the intervention group were more likely to feel well informed about reason for attending the centre.</p> <p>The earlier the booklet was received, the less confused patients felt about the visit.</p>
Johnson, 1982. ⁴³ USA II	To measure the effects of a structured patient-centred educational program on chronically ill patient's knowledge of their disease and its ramifications.	<p><i>Participants</i> 52 patients were randomly selected from a group of cancer patients who were either newly diagnosed or re-diagnosed.</p> <p><i>Types of cancers</i> Not reported</p> <p><i>Intervention</i> Patients in the intervention group (n = 26), attended eight 90 minute 'I can cope' sessions over 4 weeks given by a multidisciplinary team and access to a resource centre. The 26 patients in the control group received normal levels of support.</p> <p><i>Design</i> RCT. No information about the level of blinding is given.</p>	State Anxiety Inventory. Purpose in Life Test. A 'course inquiry' test for acquisition of factual knowledge. Use of learning resources.	Patients in the intervention group reported an improvement in mean score for levels of anxiety, mean score for knowledge, mean score for 'meaning of life' but no difference was seen in the groups' utilisation of learning resources.



Study Country Grade	Aims	Study details	Outcomes	Results
Latimer, 1998. ¹² Canada II	To examine the value of the Patient Care Travelling Record (PCTR) for improving patient mood, reducing uncertainty, increasing satisfaction with care, decreasing health care utilisation and maximising pain control.	<p><i>Participants</i> 21 palliative care patients completed the trial out of 46 recruited from one palliative care program over a 2 year period; patients were aware of their diagnosis; all had prognosis > 2 months; eligibility rate 20%, equal numbers of males and females. Mean age 55;</p> <p><i>Types of cancers</i> Not reported.</p> <p><i>Intervention</i> Patients in the intervention group were given the PCTR. This document provides information about the patient's illness; treatment and care, those involved in the patient's care, information relating to the patient and their families understanding of their illness, treatment decisions and suggested therapies for symptom control. It was completed by the palliative care nurse or physician and reviewed by the patient and their family/caregiver.</p> <p><i>Design</i> RCT.</p> <p>Both groups completed identical questionnaires at baseline, then 1 to 2 months follow-up.</p>	<p>Structured ratings scales assessed.</p> <p>Pain severity on the day of measurement and for the preceding week.</p> <p>Mishel Uncertainty of Illness Scale.</p> <p>Profile of Mood States.</p> <p>General Satisfaction Questionnaire.</p> <p>Utilisation of health services.</p>	<p>Uncertainty at follow-up was reduced by 11% in those patients who received the PCTR. Younger patients appeared to benefit preferentially.</p> <p>No differences were noted between the control and intervention groups in terms of the mood state and satisfaction, use of health services, levels of pain in the week preceding assessment or levels of pain on the day of the assessment.</p>
Mohide, 1996. ¹³ Canada II	To evaluate the value of an information package or a mini-version in reducing distress and meeting information needs.	<p><i>Participants</i> 304 patients newly diagnosed with cancer. 41% male, 59% female. Mean age 63.</p> <p><i>Types of cancers</i> Breast - 75 Gynaecological - 78 Lung - 76 Prostate - 75</p> <p><i>Intervention</i> A 'New Patient Information Package'.</p> <p><i>Design</i> RCT of patients attending a cancer centre for the first time. Group 1 (n = 100) received new patient information package (NPIP) one week before their first appointment, Group 2 (n = 102) sent mini version of the NPIP. Group 3 (n = 102) no information package. Patients followed up 30 minutes before the clinic appointment (control).</p>	<p>Brief Symptom Inventory.</p> <p>Scherer Self-Efficacy Scale.</p> <p>A questionnaire on expectations and fears about the appointment, information preferences, understanding, usefulness of NPIP.</p>	<p>A majority of the patients in the intervention groups found the information packages easy to understand and useful. The attending relatives had similar opinions.</p> <p>The patients in the control intervention groups expressed a greater preference for receiving information before they arrived and receiving it by mail.</p> <p>No difference was found in levels of psychological distress, preferences for receiving information (98% overall) or effectiveness between the two packages.</p>

Study Country Grade	Aims	Study details	Outcomes	Results
Ong, 2000. ¹⁴ The Netherlands II	To assess the effect of access to audiotape of patient's initial consultation with oncologist in terms of patient satisfaction, recall and quality of life	<p><i>Participants</i> 201 patients who all were aware of their diagnosis of cancer. All were referred to gynaecological or medical oncology clinic.</p> <p><i>Types of cancers</i> Gynaecological - 70%, Other - 30%.</p> <p><i>Intervention</i> Immediately after consultation, patients allocated to the intervention group were given an audiotape of the consultation.</p> <p><i>Design</i> Double blind RCT. Questionnaire follow-up at one and 12 weeks after consultation.</p>	<p>Recall Questionnaire.</p> <p>Patient Satisfaction Questionnaire.</p> <p>Quality of Life – Rotterdam Symptom Checklist.</p> <p>Medical Outcome Studies.</p>	Patients in the intervention group reported an improvement in recall of diagnosis, prognosis, operation details, details of radiotherapy, alternative treatment, side effects and consequences ($p < 0.001$). They reported improved recall of trial procedure and chemotherapy ($p < 0.01$) and in overall satisfaction with the consultation ($p < 0.01$).
Benor, 1998. ¹⁵ Israel V	To measure the effect of a structured nursing intervention aimed at empowering the patient by giving them the relevant specific knowledge, support and skills to deal with their own care and symptoms.	<p><i>Participants</i> 94 ambulatory patients with no evidence of metastases. Patients were aged between 20 and 70 years. They were treated with chemotherapy and/or radiotherapy. 23% male, 77% female. 40 nurses self-selected who took part in a 6 month course and passed an oncological knowledge test.</p> <p><i>Types of cancers</i> 56 Breast - 56 Intestinal - 19 Genital - 7 Lymphomas - 12</p> <p><i>Intervention</i> Patients in the intervention group were visited at home by a nurse for 1 to 2 hours for 3 successive months. The patient and nurse completed a symptom control assessment and rated other complaints. At the visit the patients were given relevant knowledge, support and guidance and encouraged to generate their own solutions to problems.</p> <p><i>Design</i> Quasi-experimental design with patients attending an oncology day centre between 1992 to 1994. It was partially randomised and matched.</p>	<p>Symptom Control Assessment (SCA) designed for the study and consisting of 16 symptoms and complaints specific to cancer patients, 8 basic, universal needs subdivided in to 13 elements (pain, anxiety, self-image and sexuality, rates the level of intensity, independence, perception of help from others and knowledge).</p>	<p>A decrease in intensity of all symptoms was noted, except respiratory symptoms among those in the intervention group. Those in the control group showed no difference other than an increased level of anxiety.</p> <p>An increase in independence as measured by 13 of 16 symptoms, was noted in the intervention group while the control group required extra help with 11 of 16 symptoms.</p> <p>The patients' perception of help was increased in the intervention group but decreased in the control group.</p> <p>In the intervention group, the patients' knowledge of each symptom increased but this was not seen in the control group. Among these patients the level of knowledge actually decreased in relation to three symptoms.</p> <p>At follow-up, the patients in the intervention group had an improved symptom profile in relation to body image, sexuality, anxiety and fluid intake.</p>



Study Country Grade	Aims	Study details	Outcomes	Results
Butow, 1998. ¹⁶ Australia VI	An exploratory study to investigate factors which influence patient's satisfaction and utilisation of cancer information booklets and to investigate factors which may influence these outcomes.	<p><i>Participants</i></p> <p>Stage 1 - 36 consecutive patients undergoing chemotherapy for malignancy. 19% male, 81% female. Mean age 50.</p> <p>Stage 2 - A second sample of 24 cancer patients undergoing chemotherapy for malignancy and who had been given one of two booklets as part of the treatment. 25% male, 75% female. Mean age 49.</p> <p><i>Types of cancers</i></p> <p>Stage 1 50% breast. 29% gynaecological. 21% other.</p> <p>Stage 2 58% breast. 22% gynaecological. 19% other.</p> <p><i>Intervention</i></p> <p>Stage 1:- 5 commonly used cancer information booklets were given to cancer patients in New South Wales (NSW) hospitals. Each contained information about chemotherapy but their focus differed.</p> <p>One booklet was specific to drug therapy (Booklet 1), one contained practical information about coping with chemotherapy (Booklet 2), one was aimed at understanding chemotherapy, one concerned problems that may occur during therapy and the last booklet detailed the nature of cancer, treatment and the cancer unit.</p> <p>Stage 2:- Booklet 1 and 2 as above.</p> <p><i>Design</i></p> <p>Cross-sectional survey of patients receiving chemotherapy or who had recently received at least 2 cycles of chemotherapy at a university teaching hospital.</p> <p>Stage 1:- A structured postal questionnaire was sent to patients.</p> <p>Stage 2:- Patients were sent a postal questionnaire 2 days after the booklet had been given to assess the relationship between preference for information style, satisfaction and recall.</p>	<p>Stage 1: Patients were asked to rate satisfaction, preference, utilisation (booklet 1 & 2 only) and readability.</p> <p>Stage 2: Rating of information preference style. Satisfaction. Extent to which the patient had actively sought information.</p> <p>Amount of information the patient desired. Recall assessed with 20 open ended and multiple choice questions.</p>	<p>Stage 1: No differences were seen in satisfaction levels for the various booklets. Satisfaction with all booklets was high. Booklets 1 & 2 were well utilised by patients and their families.</p> <p>Stage 2: The amount of information in booklets 2 & 3 was preferred. Booklet 2, written at grade level 8, was ranked highest for understanding. The patients preferred to receive booklets before treatment. Most patients wanted general cancer information at the treatment decision stage, however, 11-25% stated they would like booklets after diagnosis.</p> <p>Stage 2: Irrespective of information preference style or the extent to which the patient sought or desired information, patients were satisfied with the information given. There were no differences in recall between patients with high and low preference for information. 54.2% of those who received booklet 1 and 55% of those who received booklet 2 preferred to receive them at the time of treatment decision. A third of patients preferred to receive information immediately prior to their therapy and 10% of patients preferred information to be given at the time of diagnosis.</p>

Study Country Grade	Aims	Study details	Outcomes	Results
Derdiarian, 1989. ¹⁷ USA VI	To assess the effects of an individualised educational/ counselling intervention on patients' and their spouses' satisfaction and ability to cope with cancer.	<p><i>Participants</i> 60 recently diagnosed male patients with a first-time diagnosis of non-terminal cancer who were not yet receiving treatment. The mean time since diagnosis was 7 days. No significant differences were noted between the trial arms.</p> <p>Patients were recruited from a clinic in one cancer centre.</p> <p><i>Types of cancers</i> Melanoma - 32 Sarcoma - 21 Colon - 7 Testicular - 1. Age range - 25 to 55, mean age 41.</p> <p><i>Intervention</i> Those in the control arm received routine verbal and written informal information, counselling or follow-up care as requested or if indicated by the informational needs assessment, from the clinic (n = 30). Those in the intervention arm received individualised formal information, counselling, follow-up care and referral as indicated by informational needs assessment; literature published by the American Cancer Society; information relating to other agencies and when and how to contact them (n = 30).</p> <p><i>Design</i> A repeated measures design.</p> <p>1 to 2 follow-up telephone calls to check the adequacy of the information.</p> <p>All participants and spouses completed informational needs and satisfaction instruments independently at baseline and 5 to 10 days later.</p>	Patient Informational Needs Assessment. Spouse Informational Needs Assessment. (Both measure disease, personal, family and social informational needs on a 10-point rating scale.)	<p><i>Pre-intervention informational needs and satisfaction</i> No significant differences observed between the control and intervention patients and their spouses.</p> <p><i>Pre/post comparisons</i> No significant differences for patients in the control group and their spouses for informational needs, coping levels or satisfaction.</p> <p>A significant difference between the control and intervention patients was found. Satisfaction and coping levels were increased for both patients and spouses. Needs assessment scores were reduced.</p> <p>Patients in the intervention group and their spouses were more satisfied with the information they received and gained more information than patients in the control group and their spouses.</p>



Study Country Grade	Aims	Study details	Outcomes	Results
Deutsch, 1992. ¹⁸ UK VI	To examine whether taping consultations improves communication with patients.	<p><i>Participants</i> 78 adult cancer patients.</p> <p><i>Types of cancers</i> Not reported.</p> <p><i>Intervention</i> Patients attending a general clinical oncology practice for a consultation where it was anticipated that difficult issues would need to be discussed were given tape of consultation.</p> <p><i>Design</i> Cross-sectional survey.</p>	Questionnaire on tape use and value of content.	Patients played the tapes a range of 1-12 times, to relatives, friends, neighbours and to GPs. All thought it was worthwhile. The amount of information contained was judged to be correct by all respondents.
Drury, 1996. ¹⁹ UK VI	To assess the acceptability of patients with cancer holding their own shared-care record.	<p><i>Participants</i> 34 patients with progressive cancer and a prognosis of three months or more. 62 % male, 38% female Mean age 65</p> <p><i>Types of cancers</i> Not reported</p> <p><i>Intervention</i> All patients were given a shared care record detailing appointments, medication, carers' addresses and contact telephone numbers, the contact address of support organisations and a diary of significant events to be completed by patients and carers.</p> <p><i>Design</i> Observational study of out-patients recruited over 13 week period in 1992 from a hospice and three general practices. Two patient interviews were carried out after entry, at 4-6 weeks and 10-12 weeks. Additionally, carers were interviewed at 10-12 weeks.</p>	In-depth, semi-structured interviews, developed by the working group.	<p>After 4-6 weeks 41% patients were writing in their shared care records. 65% of patients read their records and 76% took it to appointments. At 10 to 12 weeks, these figures were 37%, 67% and 80% respectively.</p> <p>Professional carers use was similar after 10 to 12 weeks. Community nurses used it the least frequently however.</p> <p>Patients found the diary pages, medication pages, page of contact addresses for carers and appointments pages helpful. After 10-12 weeks the majority of patients, professionals and relatives found the record beneficial.</p>

Study Country Grade	Aims	Study details	Outcomes	Results
Glimelius, 1995. ²⁰ Sweden VI	To examine the effects of a care package in which communication played a central part.	<p><i>Participants</i> 177 patients with cancer and 120 relatives. A control group consisted of 54 patients of similar characteristics and 24 relatives. The patients were recruited from one university hospital and were undergoing chemotherapy with curative intention on one of three wards.</p> <p><i>Types of cancers</i> Breast (n = 46) Hodgkin's disease (n = 28) Non-Hodgkin's Lymphoma (n = 26) Lung (n = 49) Leukaemia (n = 23)</p> <p><i>Intervention</i> Patients in the intervention group received a care package with several interventions to improve communication; document sheets of information were given to patients, written materials were offered, an assessment and mapping of problems by interview was conducted and included interaction with medical personnel and increased relative participation was encouraged. A key nurse was identified on each ward and engaged in incidental teaching at staff meetings and staff education was encouraged.</p> <p><i>Design</i> Comparison observational non-randomised study.</p> <p>Patients were interviewed at diagnosis and at regular intervals over 2-3 months and 6 months (at the last treatment course). Relatives were interviewed at the same times.</p>	<p>Cancer Inventory of Problems Situations (CI:PS). This is a scale with 131 problem orientated statements, rated on a 4-point scale.</p> <p>'Significant others' version of CI:PS for relatives.</p>	<p>Although few patients reported problems interacting with clinical staff, the patients in the intervention group suffered fewer 'medical interaction' problems. More communication problems were experienced with physicians than nurses.</p> <p>In both groups there was a relationship between the patients' perceptions of their interaction with staff members and their level of psychosocial and marital problems. A relationship between physical problems and medical interaction was found in the control group.</p> <p>Overall relatives tended to rate problems higher than the patients. However, less problems were reported by relatives of the intervention group.</p>

Study Country Grade	Aims	Study details	Outcomes	Results
Lechner, 1996. ²¹ The Netherlands VI	To evaluate the impact of a cancer information helpline.	<p><i>Participants</i> 532 callers who contacted the helpline within a 4 week period.</p> <p>Included cancer patients (46%), their friends/relatives (37%) and the general public (17%).</p> <p>26% male, 74% female.</p> <p>Patients were significantly older than members of the other groups (mean age 52).</p> <p><i>Types of cancers</i> Not reported.</p> <p><i>Intervention</i> Provision of a cancer information line.</p> <p><i>Design</i> Retrospective evaluation of the cancer information helpline by users of the service during October 1989. During the call information was collected on the type of caller, demographics, type of cancer and stage of cancer to enable selective analysis of responses.</p> <p>A postal questionnaire was later sent to 619 callers who agreed to participate. 73% responded.</p>	A structured questionnaire measured method of communication, quality of information, communicators' skills, the degree to which the patients' needs were met and the impact of the helpline and overall level of satisfaction.	<p>The majority of users were positive about the helpline but 12% thought that it was not sufficiently accessible.</p> <p>42% of callers wanted general information. 78% of these callers reported receiving sufficient information.</p> <p>86% wanted situation specific information. 73% were satisfied with the information provided.</p> <p>72% of callers held positive opinions on the communication skills of those to whom they spoke. Patients and friends/relatives tended to view this more positively.</p> <p>94% of callers were very satisfied or satisfied, 2% no opinion while 4% dissatisfied.</p> <p>42% of callers felt that their tension had decreased while 31% stated that their fear had decreased. Most callers believed that their expectations had been met.</p>
Rainey, 1985. ²² USA VI	To assess whether preparatory education for patients receiving radiotherapy improves knowledge and reduces anxiety compared with standard information.	<p><i>Participants</i> 60 consecutive cancer patients who were undergoing their first course of radiation therapy. The were equal numbers of males and females.</p> <p>The mean age was 60.8.</p> <p><i>Types of cancers</i> 'Head and neck most frequently represented group, followed by breast, brain, cervix and prostate'.</p> <p><i>Intervention</i> Patients in the intervention group (n = 30 of 60 in total) were shown a 12-minute slide-tape program that provided information on equipment, personnel, scope of radiotherapy, procedures, introduced to staff and encouraged patients to be inquisitive.</p> <p><i>Design</i> Prospective comparison study of patients attending a cancer centre.</p> <p>Assessments 1 to 3 days after start of treatment and during the final 5 days of the 4 to 6 week period of treatment.</p>	Radiation therapy questionnaire to assess knowledge. State/Trait Anxiety Inventory. Total Mood Disturbance.	<p>At the start of treatment, patients in the intervention group showed greater accuracy of treatment-related knowledge. No significant difference between groups in affective status (anxiety levels or mood) was found.</p> <p>At follow-up, patients in the intervention group had less anxiety and lower total mood disturbance, regardless of coping style. There was no longer a significant difference in knowledge levels.</p>

Study Country Grade	Aims	Study details	Outcomes	Results
Venn, 1996. ²³ UK VI	To review the quality of a cancer information service provided by the British Association of Cancer United Patients (BACUP).	<p><i>Participants</i> 282 (69%) of callers to an information line; excluded those requiring booklets. The callers were: patients (36%); family or friends (62%); or other (2%). 20% male, 80% female.</p> <p><i>Types of cancers</i> 80 breast cancer inquiries, 326 other.</p> <p><i>Intervention</i> A cancer information service, consisting of a telephone and letter service, was offered to provide information and psychosocial support. It was staffed by trained oncology nurses.</p> <p><i>Design</i> Cross-sectional survey of callers during a 10 day period in August 1991; under sampled breast cancer inquiries so as to include other cancer types, otherwise random. Postal questionnaire sent to those who agreed to take part one month later.</p>	<p>Structured 5-point scales evaluated 7 aspects:- access, reason for calling, quality of information and suggestions, nurse's communication skills, impact and satisfaction.</p> <p>Open-ended questions were used to allow the patient to comment.</p>	<p>87% of callers had received all/almost all the information they required.</p> <p>Communication skills of the nursing staff and the content of the information given were rated positively by over 90% of callers.</p> <p>Callers tended to rate impact as 'good' and satisfaction as 'very good'.</p>
Whelan, 1998. ²⁴ Canada VI	To evaluate a cancer patient information folder designed to improve the dissemination of written information.	<p><i>Participants</i> 300 consecutive newly diagnosed cancer patients, admitted to a regional cancer centre. Mean age pre-intervention – 61.4; post-intervention – 61.8.</p> <p><i>Types of cancers</i> Breast (n = 98) Gastrointestinal (n = 52) Prostate (n = 41) Lung (n = 38) Gynaecological (n = 32) Head/neck (n = 31) Other (n = 8)</p> <p><i>Intervention</i> A personal file folder for each patient with details about written information received and pamphlets and information and support materials specific to the patient's needs.</p> <p><i>Design</i> Pre/post intervention design with random selection of allocation. Equal numbers of patients pre and post the intervention. Patients contacted over a four month period within 1 to 2 weeks of their first appointment for an assessment of existing practice. A second cohort of patients were contacted, again over a four month period and 6 weeks after the institution of the intervention.</p>	<p>Structured 15 to 30 minute telephone interview by a researcher. Patients were asked to rate understanding and usefulness of the pamphlets, their satisfaction with type and amount of information received and their preferences for information.</p>	<p>Comparison of T1 & T2.</p> <p>36% of patients received information relevant to them prior to their treatment prior to the introduction of the program. The number of pamphlets received increased after the intervention was introduced. The levels of information on chemotherapy and radiotherapy and the levels of patient satisfaction was also found to increase.</p> <p>Patient preferences for information</p> <p>27% before the first visit. 29% at the first visit. 34% as needed.</p> <p>Pamphlets relating to treatments were perceived to be more useful than those relating to support services. Each were found to be equally easy to understand.</p>



Table 3.3: Methods of training health care professionals in communication with patients with urological cancer: primary studies

Study Country Grade	Aims	Participants	Intervention	Results
Klein, 1999. ²⁹ UK II	To evaluate the immediate effects on the attitudes and skills of undergraduate medical students receiving an interview skills training programme and to assess the effects of this intervention on students performance two years later.	259 undergraduate medical students attending an interview methods course which aims to increase students awareness of the importance of doctor-patient communication, teach basic interview skills and reinforce these skills.	Intervention group were taught with cancer patients; control group was taught with patients with other diagnoses. The Attitudes Questionnaire was administered at the beginning of the course, end of course (when students were evaluated) and two years later, prior to a second evaluation. Evaluation was in the form of an interview with cancer patient which was scored with the Interview Rating Instrument by two independent researchers.	Those trained with cancer patients were more likely to introduce themselves at start of interview ($p < 0.012$), to respond empathetically ($p < 0.05$), to show regard and compassion for the patient ($p < 0.001$) and to assess the impact of the symptoms on patient's life ($p < 0.001$).
Anderson, 1982. ²⁵ Hong Kong IV	To evaluate a practical approach to teaching communication with terminally ill cancer patients.	61 medical students undertaking a second year pre-clinical Behavioural Sciences course.	Teaching formed part of student's medical training. Students were given a case scenario of a terminally ill lung cancer patient and 3 questions relating to what, how and who should inform him of his diagnosis and prognosis. Solutions were documented. In a practical session students were encouraged to discuss their solutions in small groups and to reach agreement. They watched a video where the scenario was acted out and the doctor was shown as sympathetic and 'patient centred'. They took part in a discussion with a course tutor and presented their solutions. Students completed an evaluation sheet and these were compared with their original solutions.	Prior to the training, 84% would tell the patient they had cancer and 54% would tell the patient he was going to die. 77% stated that it was the doctor's responsibility to give the diagnosis and prognosis. After the training, 38% had a change of opinion on at least 1 of the 3 questions. Those who had previously decided not to tell the patient he had cancer were most likely to change their opinion. 79% felt that they had learned from the practical session.

Study Country Grade	Aims	Participants	Intervention	Results
Maguire, 1996. ^{30, 31} UK V	To assess the impact of communication skills workshops on interviewing skills of health professionals.	206 professionals involved in cancer care. 24% doctors. 65% nurses. 7% social workers. 4% psychologists and others. Completed pre- and post-workshop assessments. 169 also completed 6 month follow-up assessment	3 or 5 day workshops were conducted in communication training and included identification of areas of concern for participants, strategies for interviewing patients and role play of interviewing a simulated patient with feedback. Assessment was by role play and occurred immediately before and after the workshops and 6 months later.	Participation in the course saw staff members increase their use of open directive questions, questions with a psychological focus and clarification of psychological aspects at follow-up assessment. There was some decline by 6 months. Significant improvements were seen in professionals' ability to elicit key patient problems and this was sustained over time. There was a reduction in the use of inhibitory actions at immediate follow-ups but there was increased use of inhibitory behaviours towards pre-workshop level at 6 months.
Faulkner, 1995. ²⁶ UK VI	To improve the communication skills of doctors in giving distressing information.	78 staff were studied. This included consultants, registrars, senior house officers, nurses and other health professionals. Participants were self-selected or nominated as requiring training.	Staff participated in a weekend residential workshop. This dealt with identifying areas of concern for the participants. Teaching, discussion on strategies for giving distressing information, discussion of problems in health care and in palliative care were included in the course. Video-taping a role-play of giving distressing information to a simulated patient was used. Feedback was by letter to participants and occurred after analysis of the interview.	After the course, 91% of the staff used a warning shot to prepare the patient psychologically for the distressing information, 85% gave the information in stages and 5% 'picked up the pieces' and attempted to find out how the patient was feeling. However, 57% questioned patients feelings but immediately blocked the response. In particular 38% blocked responses immediately after the bad news by giving information about treatment or changing the subject.
Ferrell, 1998. ²⁷ USA VI	To design and evaluate the HOPE (Home care Outreach for Palliative care Education). This is an educational program aimed at those working with the terminally ill in the community.	2 care agencies selected by the investigators were evaluated; included 52 participants. 76% nurses, 11% home health aides, 13% professionals, Mean number of years in home care 7 years. 5 project consultants with extensive palliative care experience also evaluated the program:- 2 physicians; 1 attorney/ethicist; 2 nurses.	Educational needs were assessed through a postal survey of 915 care agencies caring for the terminally ill (134 responded). HOPE was designed from this assessment. HOPE contains 5 modules; palliative care issues, pain management, symptom management, communication skills (verbal/non-verbal communication, basic skills, strategies for more effective communication) and the death event. Three 3-hour training sessions over 2 months were conducted. Learning was mainly self-directed with access to case study discussions, references and resource packs (videos, written information); training folder. Participants assessed their own program as well as the programme. Follow-up interviews with participants and agency administrators were conducted. project consultants met three times per year to review the course.	A trend for participants to perceive their effectiveness as greater post-course was seen. This was significant for pain management, the death event and cultural issues at the end-of-life care. There was a significant difference between participants' pre/post rating of the effectiveness of HOPE in all areas except for cultural issues at the end-of-life. Most participants would prefer one module to be presented at one 3 hour session. Respondents felt that the content, resource materials and participant syllabus were particularly valuable. Participants welcomed the opportunity to discuss issues with colleagues however as much of their time was spent alone.



Study Country Grade	Aims	Participants	Intervention	Results
Heaven, 1996. ²⁸ UK VI	To investigate the effect of skills training in communication for hospice nurses.	Nursing staff from 2 hospices. 44 nurses recruited. 87 patients recruited. 33 nurses completed pre- and post-intervention assessments, 22 assessed by follow-up.	A ten week teaching programme was conducted and included 2 large group sessions on skills and the assessment interview, followed by 4 small-group sessions providing individual feedback on practice tapes made with either patients, relatives, actors or colleagues. Participants were evaluated pre-course, post-course and nine months after the intervention by carrying out an audio-tape recorded assessment interview with the patient.	An improvement from pre-course to post-course and to 9 month follow-up assessment was seen in the proportion of open questions used, the number of behaviours with a psychological focus and the level of clear expression used with patients. The level of blocking behaviours increased, but this was initially lower than reported in previous studies. Little improvement was seen in the ability to identify the patient's main concern and by 9 months this had decreased to below pre-intervention levels.
Maguire, 1988. ^{32, 33} UK VI	To evaluate workshops in communication and counselling skills run jointly for doctors and nurses working in hospital and community settings with cancer patients.	218 people participated. 23% doctors, 66% nurses, 7% social workers, 4% other professionals from hospice, Macmillan, Marie Curie and other backgrounds	Staff members participated in a 3 to 4 day workshop with participation and feedback. Problems are identified by the group and teaching was by video and role play. Areas covered included basic interviewing skills, breaking bad news, patient advocacy, dealing with anger, dealing with a misinformed patient, the withdrawn patient, sudden unexpected death, challenging denial, breaking collusion and participant coping skills.	Skills of effective interaction improved after a 3 or 5 day workshop, but few participants encouraged the patient to clearly express their feelings.
Razavi D, 1988. ³⁴ Belgium VI	To evaluate the effectiveness of brief psychological training for health professionals.	165 nursing assistants, nurses, physicians, psychologists, physiotherapists, volunteers and clergy dealing with terminally ill cancer patients. (122 took part, 43 acted as controls).	Professionals took part in 12 hours of training in 4-10 sessions, each of 75 minutes to 3 hours duration. Role play and open discussion were used. Topics included coping reactions of the patient, the family and health care professionals, ethical problems and psychological management of pain.	Those who took part in the training showed significant improvements in 11 of the 20 attitudes assessed, compared with 2 of 20 in the control group. Training led to improvements in the concepts of attitude about oneself, towards illness and death, professional relationships and occupational attitudes. Most effect was seen in those who had prior negative attitudes.

Study Country Grade	Aims	Participants	Intervention	Results
Wilkinson, 1999. ³⁵ UK VI	To perform a longitudinal evaluation of a communication skills programme.	Of the 110 nurses who completed the original programme, 45% (n = 50) agreed to take part; only 33 returned usable data. No significant differences between those who took part and those in the original program were noted. Mean length of time since the original programme was 2.9 years. 6% male, 94% female. 46% employed in a hospice, 30% in hospitals, 6% in the community and 18% as specialist nurses.	Longitudinal follow-up study. Respondents were sent a letter and audio-tape cassette asking them to record a patient assessment. Feedback on the tape was given to each nurse. Their original pre/post course scores were examined. Pre-course coverage scores were low especially for psychological assessment in 88% of cases; 49% gave an adequate or good physical assessment, whereas 61% cases did so for coverage of present illness. Post-course there were improvements in all areas; these were statistically significant for introduction, patient's awareness of diagnosis, history of illness, physical assessment, psychological assessment and closure of assessment.	Overall mean score at follow-up was 15.2 compared with 10.7 (pre) and 16.3 (post). This was significant between the pre-course and post-course and between pre-course and follow-up. No significant differences between post-course and follow-up scores were found, except in the area of psychological assessment, where there was an improvement. The evaluation indicated that the course can improve levels of competency in communication skills which can be maintained
Wilkinson, 1996. ³⁶ UK VI	To evaluate a palliative care nurse-patient communication programme.	110 Registered Nurses undergoing further training. Diploma in Nursing (n = 30); Diploma in Palliative Care (n = 60); Marie Curie Advanced Award in Palliative Care (n = 20). 20 male, 90 female. Mean number of years since qualification 11.5.	26 hour training program over 6 months formed part of the nurses' courses. Training focused on knowledge, attitudes and skills with personal feedback on performance and self-critique. Participants spoke with patients on three occasions (pre-, mid- and post- course). These were recorded. 2 separate raters assessed the tapes in terms of blocking and facilitating behaviours and the depth in which 9 key areas were covered. 3 raters randomly rated 13 tapes (88% agreement). A 17-item questionnaire (the Fear of Death Scale) was administered prior to the course. The sample showed moderate levels of death anxiety.	Assessment coverage was low prior to the beginning of training, especially for psychological areas. In addition, unstructured assessments were preferred by the nursing staff. At 3 months in to the course, an improvement in assessment structure and coverage was noted. 58% assessed patients' awareness of diagnosis or prognosis and more attempts were made to elicit feelings. 3 months after course completion, the improvement in coverage was maintained. No further improvement in psychological and social assessments were seen however. The training significantly improved nurses' communication skills in 6 out of 9 key areas and especially for psychological aspects of care, handling difficult questions and illness awareness. 90% of nurses' showed improved skills, 4% remained constant and 6% showed decreased skill levels.



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Palliative Care

The Questions

- a) How effective are palliative care services in improving outcomes for cancer patients?
- b) Does rapid access or early referral to palliative care teams improve symptom control and quality of life for patients and families with urological cancer?
- c) How effective are specialist palliative care staff in multidisciplinary teams in improving communication between teams, both within settings and between settings?
- d) Is there any evidence about the optimal composition of a multidisciplinary team for patients with urological cancer?

4

The Nature of the Research Evidence

a) Palliative care services

The role of specialists in urological oncology is discussed elsewhere in this report (see Topic 1, *The Urological Cancer Network and Multidisciplinary Teams*) – but the issues specific to the palliative care of patients with urological cancer will be discussed here. Five systematic reviews, two of which are unpublished, met the inclusion criteria¹⁻⁵ (Table 4.1). One systematic review is a review of previously published reviews in this area.¹

- b) No studies that addressed this question were identified.
- c) No studies that addressed this question were identified.
- d) No studies that addressed this question were identified.

Summary of the Research Evidence

a) Palliative care services

A Dutch review of home-based palliative care programmes compared five RCTs with non-RCTs and outcome patterns were found to be similar. Home care programmes did not have a negative influence on quality of life or time spent in hospital; some included studies observed positive effects on these outcomes.⁵ Home-based palliative care lead to an improvement in pain levels, symptom control and levels of satisfaction when compared with conventional care.² While older primary studies reviewed showed poorer management of pain for patients in their homes than in the institutional environment,^{3,4} this appears to have improved in recent years.²⁻⁴

A systematic review was unable to identify groups of professionals whose involvement in a care programme consistently improved patient outcomes,³ but each study found similar or improved levels of care when a specialist palliative service managed the care of the patient.

Many primary studies have been of poor methodological quality. In some instances studies were so flawed that no results were found. Seven main methodological issues were identified by these reviews: data reporting, sample bias, data attrition, poor outcome selection, time frame of assessment, inconsistencies in services evaluated and lack of generalisability. In addition, provision of medical and social care varies between and within countries (e.g. rural and urban areas) and thus comparison of studies from different countries or areas is problematic. Consequently, even high quality systematic reviews with comprehensive search strategies and clear research questions are unable to draw many clear conclusions.

Conclusions

Overall, palliative care services appear to have a small positive effect on patients and carer outcomes and there is some evidence that conventional care alone is inadequate for patients with advanced cancer.

- b)** No studies that addressed this question were identified.
- c)** No studies that addressed this question were identified.
- d)** No studies that addressed this question were identified.

Table 4.1: Effectiveness of palliative care services in cancer: systematic reviews

Study Country Grade	Aims	Study criteria and assessment	Results	Comments
Hearn, 1998. ³ UK I / III	To determine whether teams providing specialist palliative care improve the health outcomes of patients with advanced cancer, their families or carers when compared with conventional service delivery.	<p><i>Inclusion criteria</i> Studies that considered the use of specialist teams caring for advanced cancer patients and their families.</p> <p><i>Exclusion criteria</i> Studies focusing on one cancer site were not included. This was based on the premise that overly specific studies might not be generalisable to other types of cancer.</p> <p><i>Data collection and assessment of studies</i> Data were extracted directly into tables. The studies were assessed in relation to the rigour of the study design and analysis and in relation to the appropriateness of the way the outcome measures were taken into account.</p>	<p>The review found 18 relevant studies RCTs and 13 comparative and/or observational studies.</p> <p>Four of five RCTs and the majority of the comparative studies indicate that specialist co-ordinated approach resulted in similar or improved outcomes in comparison with conventional care in relation to the patients' satisfaction levels, the patient being cared for where they wished, the family's satisfaction, the family's anxiety levels and pain and symptom control.</p> <p>No worse outcomes were associated with specialist management. While early studies showed patients being managed at home experienced more pain compared with those being managed in a hospital or hospice, this was not seen in later studies.</p> <p>One study attempted to examine the team effect as opposed to the general effect of palliative care services. No combination of health care professionals was consistently effective. A GP managing the patient without other professionals' input showed poorest outcomes.</p>	<p>Strong evidence is presented from the few RCTs and good observational studies that conventional care alone is inadequate for patients with advanced cancer. This may indicate that a multi-professional approach with specialist input is beneficial.</p> <p>Results support the use of specialist MDTs in palliative care to improve the satisfaction of patients with advanced cancer and of their family. Evidence suggests that MDTs were more able to identify and deal with patient and family needs and improved access to other services.</p> <p>Evidence of improved pain control and symptom management as a result of specialist approach was located.</p> <p>While not all studies showed an improvement, none showed adverse outcomes.</p> <p>The limitations and difficulties associated with research in palliative care are discussed.</p>
Smeenk, 1998. ⁵ Holland I / III	To investigate whether comprehensive home care programmes are more effective than standard care for patients with incurable cancer in maintaining the patients' quality of life and reducing the proportion of their time spent admitted to hospital.	<p><i>Inclusion criteria</i> Controlled prospective studies involving patients with incurable cancer.</p> <p>Studies which aimed to investigate aspects of care related to the support of patients in their own home.</p> <p>The control group had to have received standard available (home) care.</p> <p>Outcomes assessed were required to include at least one dimension of QoL or the readmission rate of patients.</p> <p><i>Exclusion criteria</i> Studies in which home care interventions aimed at one particular aspect of care – such as home parenteral nutrition/pain management.</p> <p>Studies in which the control group received only</p>	<p>The search resulted in 358 reports, of which 9, reporting 8 studies, met the inclusion criteria.</p> <p>The median methodological score was 62, showing moderate quality. The most common shortcomings were in the areas of study population homogeneity, comparability of intervention and control groups, handling of dropouts and blinding procedure for those who collected the outcome measures.</p> <p>The 5 RCTs were compared with the non-RCTs and outcome patterns were found to be similar.</p> <p>Home care programmes did not have a negative influence on QoL or time spent in hospital; some studies observed positive effects on these outcomes.</p>	<p>The effectiveness of home care programmes when compared with standard care for patients with terminal cancer remains unclear.</p> <p>The findings of the various studies failed to show a consistent pattern. However, none of the studies found a negative influence of home care interventions on quality of life or readmission time.</p> <p>Visiting patients at home and regular MDT meetings seemed to be associated with positive findings.</p> <p>The difference between the number of studies performed in USA and other parts of the world is discussed.</p>





Study Country Grade	Aims	Study criteria and assessment	Results	Comments
		<p>hospital care.</p> <p><i>Data collection and assessment of studies</i> Two investigators, independently of each other performed the search for studies and assessment of the methodological quality of studies.</p> <p>Criteria for methodological assessment of studies (study of population, interventions, effect, data presentation and analysis) based on score out of 100.</p>		
Goodwin, 2000. ¹ UK III	To identify and review all systematic reviews which evaluated palliative care services	<p><i>Inclusion criteria</i> Systematic reviews of evaluation of palliative care services examining different models of care or costs of care, across and within health care systems.</p> <p>A systematic review was defined as an overview of scientific studies that uses explicit, systematic and reproducible methods to locate, select appraise and synthesise relevant and reliable evidence.</p> <p><i>Data collection and assessment of studies</i> Two reviewers assessed and evaluated the quality of each systematic review based on established criteria.</p>	<p>Five reviews met the inclusion criteria. 39 studies in total were included in these reviews: 15 RCTs, 8 prospective studies and 16 retrospective studies.</p> <p>The mean methodological score was 8.8 of 14.</p> <p>Two reviews found similar or improved outcomes for patients' satisfaction, pain levels, symptom control and family anxiety when compared with conventional care.</p> <p>No review demonstrated an impact on QoL.</p> <p>Home care nurses' involvement was not found to have impacted on QoL.</p>	<p>None of the systematic reviews used a quantitative analysis: rather they were overviews or meta-syntheses. This prohibits statistical exploration of bias.</p> <p>A discussion of the major differences that exist in models of care in different countries is presented.</p>
Higginson, 2000. ² UK III	To determine how the palliative care team model differs from conventional care, to assess the extent to which teams have been shown to be effective and cost effective and to identify areas for future research.	<p><i>Inclusion criteria</i> Studies which investigated patients with a progressive life threatening illness and their family, carers or close friends</p> <p>Studies which assessed patients receiving a palliative care intervention from a palliative care team.</p> <p>Studies which included comparison group receiving 'usual care delivery' (e.g. general hospital and community services)</p> <p>Studies that address one or more of the following: Patient or carer outcomes. Patient, carer, professional or service processes. Specific characteristics of palliative care teams that affect outcomes and processes. The effect of late referral to a palliative care team on outcomes and processes.</p>	<p>The search identified 119 reports. Of these 44 unique studies met the inclusion criteria. The range of quality in terms of 'Method Score' was wide: 31% to 77%.</p> <p>The degree of specialisation of a palliative care team varied. There was insufficient information to judge whether there were differences between intermediate level and specialist level palliative care. There was some evidence that palliative care teams can reduce time in hospital. Overall, palliative care teams were found to have a small but positive effect on patient outcomes and carer outcomes.</p> <p>Studies of home care palliative care teams compared with conventional care indicate that pain, symptom control and levels of satisfaction are improved with home care team involvement.</p> <p>There appeared to be some substitution of hospital costs for home costs.</p>	<p>The quality of many included studies was low and the methodology and outcome variables are highly variable, making comparisons difficult.</p> <p>The methodology of research in palliative care, in terms of the evaluation of services, the measurement of outcomes and the assessment of economic effects needs to be substantially improved.</p> <p>Research in palliative care is difficult to conduct and should be sensitive to the needs of patients with advanced illness and their families.</p>

Study Country Grade	Aims	Study criteria and assessment	Results	Comments
		<p><i>Exclusion criteria</i> Reports of individual case histories. Reviews without interventions. Needs assessment without intervention. Reports which described but did not evaluate an intervention. Studies of care or therapies not usually defined as 'palliative' such as surgery.</p> <p><i>Data collection and assessment of studies</i> Studies assessed for inclusion and quality by six researchers. Quality assessment was by means of calculation of a 'Method Score' based on clear definitions of aims and outcome measures.</p>		
Salisbury, 1999. ⁴ UK III	To identify and review all experimental and descriptive studies which evaluated a model of specialist palliative care, using quality of life as an outcome measure.	<p><i>Inclusion criteria</i> QoL was interpreted to include formal measures and measures of pain control and symptom control as well as general well being. Only studies conducted in Europe, North America, Australasia or Israel since 1978 were included.</p> <p><i>Exclusion criteria</i> Studies were excluded if they were based on personal opinion, individual case histories or a discussion of ethical, legal or educational issues, if they assessed the impact of chemotherapy, radiotherapy or surgery on QoL, if they assessed psychometric QoL scales or if they assessed the impact of palliative care on the QoL of relatives or carers.</p> <p><i>Data collection and assessment of studies</i> Data were extracted onto a pre-designed data extraction sheet and entered onto an access database. No formal quality assessment was used owing to the wide variation seen in the types of studies located.</p>	<p>86 relevant studies were located. 22 reported descriptive studies, while 27 reported comparative studies; only these were included in the review.</p> <p>Inpatient specialist palliative care was found to result in better pain control compared with home care or conventional care in old studies. This was based on methodologically weak research not supported in all studies. Follow-up studies showed pain control to have improved in both hospice and general hospitals but with the magnitude of the difference reduced over time.</p> <p>Limited evidence found suggests that hospital palliative care support teams can improve pain control for patients dying in hospital, but no evidence was found on whether they impact on other QoL measures.</p> <p>It was not demonstrated that palliative home care teams, co-ordinating nurses or advisory teams have an impact on the QoL of patients dying at home. A recent study provided evidence that community-based specialist palliative care is beneficial in terms of pain control however.</p>	<p>A dearth of good quality evidence on which to base any conclusions was noted.</p> <p>Most of the published material identified was based on opinion and had little scientific/evidential support.</p> <p>The overall conclusion was that there is little robust evidence that any form of organisation of specialist palliative care offers significant advantages on the impact of patients' QoL.</p> <p>Several of the studies showed improvements in terms of patient satisfaction or costs. Some evaluations have however used inappropriate outcome measures. The difficulties of conducting research on the effectiveness of palliative cancer care are discussed.</p>



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Prostate Cancer

The Questions

- a) How effective are treatments for patients with early (T1 to 2, N0, M0) cancer of the prostate in terms of disease control, adverse effects and quality of life?
- b) How effective are treatments for patients with locally advanced (T3 to 4, N0, M0) cancer of the prostate in terms of disease control, adverse effects and quality of life?
- c) How effective are first-line systemic treatments alone for patients with locally advanced or metastatic prostate cancer (bone, lymph node or viscera) in terms of disease control, adverse effects and quality of life?
- d) How effective are second-line treatments for patients progressing after androgen ablation therapy?

The Nature of the Research Evidence

a) **Early prostate cancer**

Questions on the relative efficacy of different forms of radical treatment of early prostate cancer are unanswered by any large-scale RCTs.

Several systematic reviews of one or more aspects of the three major primary management strategies – radical (total) prostatectomy; external beam radiotherapy (EBRT);¹⁻¹² and active monitoring (also termed watchful waiting or surveillance) have been identified. Most of the reviews are subsumed, however, in other reviews.^{6-11, 13} One review compared outcomes after EBRT and surgery.¹⁴ Prostate cancer patients were included in one review of randomised trials of fast neutron therapy.¹⁵ Details of the reviews of studies on the management of localised prostate cancer are contained in Table 5.1a.

A single RCT comparing radical surgery and radical radiotherapy for suitable patients with non-metastatic prostate cancer has been published¹⁶ and the results subsequently updated.¹⁷ A single randomised trial comparing radical surgery to 'placebo' has been presented.¹⁸

Four additional primary studies were located¹⁹⁻²² (Table 5.1b). One registry-based study presented survival data on men treated with surgery, radiotherapy and conservative management.²² Additionally, three series reporting the results of brachytherapy were located.¹⁹⁻²¹

No randomised trials comparing brachytherapy with other treatment modalities have been identified. However, a proposed randomised trial of brachytherapy compared with radical prostatectomy is in development in North America. Four systematic and non-systematic reviews of observational studies of brachytherapy were identified²³⁻²⁶ (Table 5.1a). Morbidity has also been described in several

prospective and retrospective studies published since these systematic reviews.²⁷⁻³² Biochemical outcomes were investigated in two studies.^{20, 21}

The earliest UK publication on active monitoring has been included as a historical illustration.³³ Two randomised trials of standard dose as against high dose EBRT were identified^{34, 35} (Table 5.2).

One study has examined competing causes of death in prostate cancer patients relative to their age and to their disease characteristics.³⁶ Four highly relevant RCTs are in progress:

- The European Prostate Cancer Screening Study.
- The PIVOT Study comparing radical prostatectomy with active monitoring, shortly to be completed in the United States.³⁷
- A similar design study in Scandinavia has finished accrual (n = 695) and will shortly publish the five year mean follow-up results.
- The ProtecT Study, funded in the United Kingdom, which will combine the identification of men with prostate cancer detected by PSA screening with a randomised trial of radical surgery, radical external beam radiotherapy and active monitoring.

The MRC PR06 study randomising patients between active monitoring, radical surgery and radical radiotherapy, was closed in 1997 owing to poor accrual.¹ In addition to the comparative studies of different modalities listed above, there are ongoing studies looking at techniques of radical surgery and radical radiotherapy (such as the MRC RT01 study, which is to report in around two to three years' time).

One systematic review of non-surgical treatment for post-prostatectomy incontinence was found³⁸ (Table 5.3). Two randomised trials of conformal radiotherapy compared with conventional radiotherapy, in which morbidity was an endpoint, were found.^{39, 40} Morbidity of radical therapy has also been described in several non-randomised studies. Details of these are incorporated in a systematic review of the incidence of morbidity following radical radiotherapy⁴¹ (Table 5.4a). A registry-based study on the morbidity associated with radical prostatectomy was located⁴² (Table 5.4b).

Three studies have been included which address causes of bias in assessing outcomes after treatment for prostate cancer.⁴³⁻⁴⁵

b) Locally advanced disease

Three reviews were located⁴⁶⁻⁴⁸ (Table 5.5a). A systematic review examined all of the (then) current randomised trial data together.⁴⁶ A retrospective individual patient data analysis of the RTOG database has examined the effects of long-term or short-term hormone therapy in combination with radiotherapy, taking data from RTOG randomised trials, though the original trial randomisations did not correspond to the comparisons made in this re-analysis.⁴⁷ In addition, the data on randomised trials of radical prostatectomy with or without hormone therapy have been analysed in a systematic review.⁴⁸ In addition, a number of primary studies were located (Table 5.5b). Seven randomised trials compared

radiotherapy alone with radiotherapy and hormone therapy.⁴⁹⁻⁵⁵ The MRC study was the only study to include a hormones-alone arm.⁵² A more recent non-randomised comparison of long-term androgen suppression with EBRT – the RTOG 92-02 trial⁵⁶ – was not incorporated in that report. Information was located on the first analysis of data from three randomised trials of radical prostatectomy, radical radiotherapy or active monitoring with or without adjuvant bicalutamide and on the tolerability of bicalutamide.^{57, 58}

c) Systemic treatment

One meta-analysis has reviewed the efficacy of different forms of hormone therapy for metastatic disease compared with orchidectomy in randomised trials⁵⁹ (Table 5.6a). Part of a larger review addressing the management of prostate cancer, reviewed evidence comparing monotherapy with orchidectomy⁶⁰ (Table 5.7a). In addition, one primary study which compared monotherapy with orchidectomy was located⁶¹ (Table 5.6b).

One meta-analysis of randomised trials of immediate compared with delayed hormone therapy was found⁶⁰ (Table 5.7a). The Prostate Cancer Trialists Group (PCTG) has also carried out a meta-analysis of immediate compared with deferred anti-androgen therapy, with individual patient data analysis. It is to be updated in 2002. This study was presented in 1997 but has not been published and the results are not available for comment. However, the MRC randomised trial of immediate compared with deferred hormone therapy study⁶² (Table 5.7b) was one of the larger constituent studies of PCTG meta-analysis. This study has been further analysed and published in abstract form only.⁶³ A randomised trial of immediate (adjuvant) hormone therapy compared with observation in men with node positive disease following radical prostatectomy has been reported recently⁶⁴ (Table 5.7b). Additionally, a trial which assessed quality of life outcomes was located.⁶⁵

Maximal androgen blockade (MAB – also known as combined androgen blockade or CAB) has been the subject of a number of meta-analyses and systematic reviews^{60, 66-77} (Table 5.8a). One additional primary study was also located⁷⁸ (Table 5.8b). Statistical issues pertinent to MAB trials were considered in a recent commentary.⁷⁹ No systematic review or randomised trial of anti-androgen withdrawal after progression on first line hormone therapy was found.

d) Second-line treatment

In a proportion of patients who have hormone or anti-hormone therapy discontinued, an objective response to the altered hormonal environment is noted. Two studies addressed this phenomenon.^{80, 81}

Three systematic reviews were located⁸²⁻⁸⁴ (Table 5.9a). One systematic review of randomised trials comparing Strontium-89 therapy with other modalities was found.⁸² Further systematic reviews of both randomised and non-randomised studies of Strontium-89 have also been performed.⁸³⁻⁸⁴ Two RCTs assessed radiotherapy for bone pain^{85,86} (Table 5.9b).

One systematic review has examined the efficacy of chemotherapy, in a heterogeneous group of studies⁸⁷ (Table 5.10a). Two randomised trials have compared mitoxantrone and corticosteroids with corticosteroids alone^{88, 89} and

one randomised trial compared orchidectomy alone with orchidectomy and mitomycin⁹⁰ (Table 5.10b).

Three studies of taxanes were located. Two investigated the combination of paclitaxel and estramustine.^{91, 92} The other study investigated the single agent use of docletaxel.⁹³

More recent forms of therapy for which randomised trials have been identified include the matrix metalloproteinase inhibitor prinomastat/AG3340,⁹⁴ atrasentan/ABT-627⁹⁵ and the bisphosphonates clodronate,⁹⁶ zoledronate,⁹⁷ and alendronate.⁹⁸ In addition, one randomised trial has examined the effects of the bisphosphonate pamidronate on bone mineral density in patients treated with hormone therapy⁹⁹ (Table 5.11).

Other agents, not the subject of RCTs, include PC-SPES, which was not considered in detail.¹⁰⁰

Modalities that are more rarely used (e.g. cryotherapy, hypothermia) were not included in this review as no RCTs have been identified and the existing studies are of small scale. However, cryosurgery has been reviewed by the Agency for Healthcare Policy and Research.¹⁰¹

5

Summary of the Research Evidence

a) Early prostate cancer

No consistent evidence has been reported for the inherent superiority of any of the three means of radical therapy for localised prostate cancer – external beam radiotherapy (EBRT), brachytherapy and radical prostatectomy (RP), in terms of their efficacy. A comprehensive review published in 1997 covered the aetiology, diagnosis, treatment, economic evaluation and screening for early localised prostate cancer.¹ An extensive electronic search was conducted for publications between 1990 and 1995. Economic searches included studies conducted after 1986. Details of the search and quality assessment strategies were given. Another report² covered a similar range of topics and advanced disease. No search strategy or quality assessment strategy was given.

It has long been realised that some patients managed by active monitoring, (surveillance, watchful waiting or expectant management) will experience disease progression.³³ What is not clear and the available data do not clarify, is whether early treatment affects overall survival and if so, whether there is an optimum form of radical (curative) treatment. The two published randomised trials in this area¹⁶ were included in a review commissioned by the HTA and were criticised for a number of methodological flaws.¹ Neither study has answered the specific question that they set out to address. The update¹⁷ of the earlier study¹⁶ indicates a very high biochemical failure rate after radiotherapy. This is at odds with observational studies of the effects of EBRT.

The relative efficacies of radiotherapy and surgery were reviewed based on a search for articles published up to 1993.⁴ A search strategy was provided and the articles independently assessed for quality. There were wide ranges in the reported outcomes after radiotherapy.

This compares with a review, again based on a search of articles published between 1986 and 1997, which showed similarly wide ranges in outcome after external beam radiotherapy.⁵ This study was based on series where pre- and post-treatment PSA levels were recorded, but no quality assessment criteria were given and there were substantial differences in the definitions of 'biochemical control' of disease across the constituent studies.

A study based on a search from 1990 to 1996 compared the outcomes of EBRT and surgery.¹⁴ The principal outcome measure was biochemical control, though this was ill defined for EBRT patients. There appears to be a number of methodological and interpretative problems with this study.

A number of studies were conducted for the American Urological Association.⁶⁻⁹ These attempted to define the evidence base to underpin recommendations on the management of localised disease. They were based on searches of articles published between 1966 and 1994, supplemented by hand-searching and access to individual panel members' libraries; no details were given of the inclusion criteria or quality assessment.

One review was based on a search of articles published between 1996 and mid 2000. Though not systematic, it is the most up to date of the reviews available on radiotherapy and details of the search strategy and inclusion/exclusion criteria were given.³

The largest single observational study was prepared by the SEER group.²² This was a population-based study using data from nine US registries and a total of 59,876 men managed by radiotherapy, surgery or conservative management. This study is based on a very robust database subject to rigorous quality control, but it was not possible to include variables such as PSA levels, as the data collection began before PSA monitoring was widely available. The endpoint of overall survival and the starting point in terms of tumour grade are robust and of high quality. However, this study is unable to account for selection bias between the management options, for PSA level at diagnosis and for salvage or other therapies given after the initial management decision was made. Therefore, attempts to use the SEER data to compare the efficacy of the three management options must be treated with extreme caution.

The role of brachytherapy in disease control has been addressed in the previously discussed reviews,^{5, 12} in the report by the health technology assessment council of Quebec, Canada,²⁴ in other systematic reviews^{23, 25, 26} as well as additional primary studies.¹⁹⁻²¹

The Canadian report was based on a search for articles published between 1972 and 1999, but no search strategy was provided. Studies were independently assessed and ranked using standardised criteria. In this study, variations were seen in the clinical, biochemical and biopsy-based disease control rates.²⁴ One systematic review was based on a very comprehensive search of articles published between 1997 and 1999.²⁶ Each study was assessed and the data extracted independently. The other systematic study evaluated brachytherapy in localised prostate cancer using data from 16 studies.²³

Of the observational studies published since these reports were written, among the longest follow-up was ten years.²¹ Other retrospective studies underline the need for a randomised trial. For example one study suggested that

brachytherapy was equivalent to EBRT for patients with favourable prognosis prostate cancer, but inferior to EBRT for patients with a poorer prognosis.²⁷

In making any assessment of relative efficacy, several problems are inherent in all the studies so far described, underlining the need for a large randomised trial if reliable evidence is to be obtained:

- Selection criteria may be of paramount importance in determining outcome, but it is difficult or impossible to determine the factors which lead to the selection of one modality over another. In addition, there may be other biases.⁴³⁻⁴⁵
- Case-mix may be a particular problem in the interpretation of prostate cancer studies, with particularly wide variations in competing relative risks of death from prostate cancer and from other causes in men managed by conservative treatment, as demonstrated by an analysis from the SEER database.³⁶
- Techniques in surgery have evolved and improved over the past decade, with procedures such as nerve-sparing radical prostatectomy. This could impact on outcomes.
- Techniques in EBRT have evolved with the introduction of high-dose, conformal radiotherapy and with the anticipated introduction of intensity modulated radiotherapy to the UK. Because the development of these techniques is recent, there are few long-term outcome data associated with their use.
- Techniques in brachytherapy have evolved, with the introduction of linked seeds and with changes in dosimetry policies reducing the dose delivered to the prostatic urethra, both of which may reduce morbidity.
- Overall survival, a key outcome in many areas of cancer treatment, may not be reliably determined for ten or even 20 years, owing to the long natural history of prostate cancer. Many publications therefore report surrogate endpoints such as no evidence of disease clinically (cNED), no evidence of disease biochemically (bNED), clinical progression free survival and disease specific survival. The validity of these endpoints is not proven.
- Many radiotherapy studies in recent years have incorporated adjuvant hormone therapy, following the EORTC study.⁵⁰ (For further discussion of this study, see section (b).)

With these problems in mind, the following statements can be made from the evidence presented above and in Table 5.1a and Table 5.1b:

- i. There is no clear evidence that any of the three treatment modalities (RP, EBRT and brachytherapy) are inherently superior to one another in terms of efficacy.
- ii. Patients with high grade tumours suffer more adverse events (disease progression, prostate cancer deaths) than patients with moderately or well-differentiated tumours.^{11, 22}

- iii. There is no firm evidence that survival rates after EBRT, RP or brachytherapy for patients with any grade of tumour are significantly different to the survival rates after active monitoring.^{1, 11, 22} This justifies the inclusion of active monitoring as a randomisation arm for all men in the ProtecT study, irrespective of their age or the tumour grade. While the apparent lower 10-year survival rates in conservatively managed patients, compared with radically treated patients in the SEER study could be interpreted as indicating the superiority of radical therapy for this group of patients, the patients were not randomised. This may be affected by biasing factors such as those discussed above or the clinical stage or PSA level. These differences could not be accounted for in the SEER data.

The individual morbidities of RP, EBRT and brachytherapy have been well described.

A study of the US Medicare database identified 2,124 men who underwent prostate brachytherapy in 1991.¹⁹ This study has the advantage that the data are relatively mature, but the caveat is that brachytherapy techniques have improved over the past ten years. Similar comments apply to the morbidity data in the study using Canadian data²³ and others.²⁹ Morbidity in the first year after brachytherapy has, however, been described in an observational study of recently treated men. This study indicates significant urinary morbidity during the first three to six months, declining thereafter to near baseline levels by one year.^{31, 32}

One study estimated impotence rates after a physician assessment, a technique which the authors state has been validated, but it is nonetheless a distinct technique from the self-administered questionnaire referred to above.³⁰ Reported impotence rates following brachytherapy do, however, compare favourably with other modalities, but such comparisons have thus far only been made on unrandomised data and are subject, therefore, to potential bias.^{29, 30} One prospective study has suggested that erectile dysfunction is worse in patients treated with both brachytherapy and EBRT than in patients treated by EBRT alone.²⁸ As with efficacy, the morbidity of brachytherapy needs to be formally compared with other modalities in a prospective, randomised study, such as that proposed by the National Cancer Institute of Canada.

Preliminary data from RCTs suggests the possibility that increased EBRT doses using conformal therapy may result in improved biochemical disease control compared with lower doses.^{34, 35} However, in neither of these trials was the advantage to high dose therapy significant by conventional statistical criteria. Confirmation from studies analysing more mature data from these and other ongoing randomised trials is awaited. One of these studies randomised 305 patients to 70Gy or 78Gy of radiotherapy; the other, an MRC study, was a pilot randomised trial for the RT01 study and was of similar design. The MRC RT01 trial is a randomised trial comparing standard dose (64Gy) with high dose (74Gy) conformal radiotherapy. It closed to accrual in 2001 with around 800 patients randomised. Other approaches such as fast neutrons, which have been previously tested in phase III studies, have not been followed up further in prostate cancer.¹⁵

In general terms, EBRT has been reported to cause more bowel toxicity, but less incontinence than RP, while brachytherapy has been reported to have a similar or superior toxicity profile compared with either of the other forms of treatment. The morbidity of EBRT has been evaluated in a number of studies. However, many do not make a clear distinction between acute side effects and long-term side effects.⁶ This is an important distinction, as acute side effects are common, often treatable and are self-limiting, whereas late side effects are uncommon, but permanent. There is high quality evidence that conformal EBRT reduces acute⁴⁰ and late bowel morbidity.³⁹

All three modalities are known to be associated with erectile dysfunction. A systematic review of erectile dysfunction after EBRT and radical prostatectomy suggests that impotence rates are higher after surgery (58%) than after radiotherapy (31%).⁴¹ No search strategy was provided for this study, but each article was subject to quality assessment; the study was based on articles published between 1970 and 1994.

A random sample of 1,291 men from the SEER database, stratified for age and ethnicity factors and treated by radical prostatectomy, was analysed to assess the degree of urinary and sexual dysfunction following radical prostatectomy.⁴² In contrast to more recent studies, this was based on a patient administered, rather than a physician administered questionnaire and substantial rates of urinary and sexual problems were identified.

The optimum treatment of post-prostatectomy incontinence is unclear, but pelvic floor muscle training, with or without biofeedback in comparison with no active treatment was assessed in a systematic review which located five randomised trials.³⁸ However the results were inconclusive.

Conclusions

There is no evidence as to whether or not radical treatment improves survival for men with organ-confined prostate cancer and surgery, external beam radiotherapy and brachytherapy. All have side effects. Nonetheless, radical therapy may delay disease progression and technical improvements in all modalities have taken place over the last ten to 20 years. However, absence of evidence is not evidence of absence and the outcome of studies such as the Swedish randomised trial of radical prostatectomy compared with active monitoring, shortly expected, are of the utmost importance.

b) Locally advanced disease

In interpreting the evidence from randomised trials using adjuvant or neo-adjuvant hormone therapy, in combination with EBRT or RP, there are a number of issues which must be borne in mind:

- Surrogate outcome measures for overall survival have been used in many studies.
- The evidence suggests there may be an overall survival benefit for treating some patients with non-metastatic prostate cancer, with a combination of radiotherapy and hormone therapy, compared with radiotherapy alone⁵⁰ although this conclusion sometimes has been based on sub-set analysis.^{49, 51}

- Randomised trials comparing EBRT or RP with or without hormone therapy did not have an androgen ablation therapy alone arm, with the exception of the MRC PR02 study.⁵² When there is no hormone only arm, it is not possible to say with certainty whether the benefits that appear in patients treated with combined modality therapy are owing to the combination or to the androgen ablation *per se*. The MRC PR02 study randomised 277 patients with prostate cancer and no bone metastases to orchidectomy alone, radiotherapy alone or a combination of the two. This study showed no overall survival benefit for androgen ablation alone or with radiotherapy, but did show a delay in time to metastasis in patients treated with hormone therapy (with or without radiotherapy). This study was however too small to detect smaller, clinically relevant differences in overall survival. There is an ongoing RCT (NCIC/MRC PR3/PR07), which may help to address this issue.
- Studies of immediate compared with deferred hormone therapy, apart from those discussed above, suggest that immediate hormone therapy leads to a reduction in disease specific events (e.g. improved progression free survival, improved bNED). However, this benefit does not appear to equate with an improvement in overall survival of similar magnitude. The reasons behind this observation need to be further elucidated. At the present stage it is difficult to determine the impact that this finding should have on healthcare policies.

Three systematic reviews which pertain to the use of neo-adjuvant hormone therapy were located.⁴⁶⁻⁴⁸ In addition, seven randomised trials have suggested benefits in terms of surrogate outcome measures, for patients treated with various combinations of EBRT and hormone therapy.⁴⁹⁻⁵⁵

Improvements in overall survival have been reported in the EORTC study in which 415 patients with predominantly locally advanced prostate cancer were randomised to receive either radiotherapy alone or radiotherapy with hormone therapy.⁵⁰ In this study, hormone therapy was started on the first day of radiotherapy and continued for three years. The results showed an improvement in five year disease-specific survival (85% compared with 48%, $p < 0.001$) and an improvement in overall survival (78% compared with 62%, $p = 0.001$) in favour of those patients managed by combined therapy.

In a smaller study performed in Sweden, 91 patients with prostate cancer were randomised to EBRT alone or EBRT and orchidectomy following after surgical lymph node staging.⁵³ Benefits to combined modality therapy were seen in terms of disease progression (61% compared with 31%, $p = 0.005$), cause-specific survival (44% compared with 27%, $p = 0.06$) and overall survival (mortality 61% compared with 38%, $p = 0.02$).

Improvements in overall survival are also reported on analysis of RTOG 85-31;⁴⁹ this was however an analysis of subgroups of patients who participated in the original trial and not of the whole population of patients. As these sub-groups were defined after the data were collected (and as such patients were not randomised to the treatments within the sub-groups analysed) the conclusion based on them must be treated with some caution.

In a study of 977 patients with non-bulky but locally advanced disease or who had pelvic or para-aortic lymph node metastases, patients were randomised to radiotherapy alone or radiotherapy with indefinite hormone therapy (beginning in the last week of radiotherapy). Improvements were seen in local failure rates (16% compared with 29%, $p < 0.001$), distant metastasis rate (17% compared with 30%, $p < 0.001$) and survival with no evidence of disease (60% compared with 44%, $p < 0.001$). However, overall survival benefits were restricted to a subset of patients with aggressive disease (Gleason scores of 8 to 10) ($p = 0.01$).

In the RTOG 86-10 trial, 477 patients with bulky primary tumours, with or without lymph node metastases, but without distant metastases, were randomised to radiotherapy alone or radiotherapy and hormone therapy commencing two months prior to radiotherapy and continuing until the end of radiotherapy.⁵¹ Improvements were seen in local control (42% compared with 30%, $p = 0.016$), in a reduction in the incidence of distant metastases (34% compared with 45%, $p = 0.04$), disease-free survival (33% compared with 21%, $p = 0.004$), biochemical disease-free survival (defined as having a PSA level below 1.5ng/ml ; 24% compared with 10%, $p < 0.0001$) and cause-specific mortality (23% compared with 31%, $p = 0.05$) for patients treated with hormone therapy and radiotherapy. Subset analysis suggested that in patients with Gleason score 2 to 6 there was a highly significant improvement in survival (70% compared with 52%, $p = 0.015$). In contrast, in patients with Gleason 7 to 10 tumours, no benefits were seen in local control or survival.

The RTOG 92-02 study randomised 1,554 patients who each received EBRT and neo-adjuvant hormone therapy to either an additional two years of adjuvant hormone therapy or no additional therapy.⁵⁶ Significant improvements were seen in disease-free survival, local progression, distant metastatic rate and biochemical failure rate in the long-term hormone therapy arm. However, the overall five year survival was not significantly different between the two arms except for a subset analysis as in the RTOG 85-31 study (see above) and in a subset comparable to those entered into the EORTC study.⁵⁰

The optimum duration of hormone therapy when given in combination with radiotherapy is being investigated in the EORTC 22961 study which is comparing short-term and long-term anti-androgen deprivation therapy in combination with radiotherapy and which is shortly to complete recruitment. Weak evidence from the RTOG database suggests that the greatest benefits, including survival benefits, may be restricted to long-term hormone therapy (3 years or more) in patients with high-grade tumours.⁴⁷ The Canadian randomised trial of EBRT alone compared with EBRT and one of two regimes of hormone therapy ($n = 120$) analysed positive biopsy rates and suggested that fewer residual cancers were detected in patients managed by the combination of EBRT and hormone therapy.

In addition, the first results of a study of adjuvant bicalutamide, in combination with EBRT, radical prostatectomy or active monitoring, have been presented. This study, a combined dataset from three international randomised trials, forms the largest RCT yet described in prostate cancer with 8,113 men entered.⁵⁸ The first reports of this study suggest a highly significant benefit in terms of a reduction in tumour progression and the development of metastasis, in patients treated with bicalutamide.⁵⁸ Overall survival analysis is ongoing in this study, but data are not expected for several years.

Seven randomised trials of neo-adjuvant androgen ablation therapy followed by total prostatectomy have been summarised in a systematic review.⁴⁸ The summary results from 1,354 patients suggests that adjuvant anti-androgen therapy reduces the incidence of positive margins following radical prostatectomy. However, it is not yet possible to say whether this surrogate outcome is clinically relevant and whether it will be reflected in improvements in other outcome measures, particularly overall survival.

Conclusions

Adjuvant or neo-adjuvant hormone therapy improves outcomes for some men, for example those with locally advanced disease, treated with radical radiotherapy. The value of adjuvant hormone therapy for men with earlier stage disease being treated by surgery or radiotherapy is ill-defined.

c) Systemic treatment

The MRC PR03 study⁶² has reported significant benefits in terms of a reduction in tumour progression and prostate cancer-specific mortality, for patients treated with immediate hormone therapy (in this study generally with orchidectomy). An initial significant survival benefit for immediate hormone therapy was also reported, which has since been subject to further analysis. This analysis, published in abstract form, indicates that the magnitude of the survival benefit for early hormone therapy has fallen with longer follow-up. While the overall survival benefit is statistically significant ($p = 0.038$), the benefit ceases to be significant when patients with M0 tumours are analysed.⁶³

A randomised trial of 98 patients found to have lymph node metastases following radical prostatectomy compared adjuvant hormone therapy with observation (equivalent to immediate compared with delayed hormone therapy).⁶⁴ This study suggested delayed progression and a reduction in deaths from prostate cancer in patients treated with immediate hormone therapy.

In general terms, the published findings of the first analysis of the PR03 study⁶² closely mirror findings from another analysis.⁶⁰ Other studies, including the EORTC 30891 and 30846 studies, expected within the next three years, will provide substantial amounts of information on this subject.

One interpretation of the results of the MRC PR03 study is that the quality of monitoring for patients who were randomised to deferred hormone therapy was variable and that this may have contributed to the outcome. It is important, also to note that the reported survival benefit for early hormone therapy may not be maintained on further analysis. This could indicate that early hormone therapy has other, adverse effects and further studies are needed to investigate this possibility. Furthermore, such survival benefits could reflect a better standard of medical intervention in patients managed with immediate therapy who would otherwise have been at imminent risk of developing severe disease complications.

The options for androgen ablation therapy include orchidectomy, LHRH analogues, non-steroidal anti-androgens, steroidal anti-androgens and MAB, the latter using non-steroidal anti-androgens or steroidal anti-androgens in combination with LHRH analogues or orchidectomy.

A number of studies were identified, assessing, summarising, or in three cases performing a meta-analysis, of randomised trials of maximal androgen blockade (MAB) compared with monotherapy.^{60, 66-69, 71-76, 78}

The Prostate Cancer Trialists Group (PCTG) pooled data on all forms of MAB.⁷⁰ The analysis may be criticised on the basis of patient heterogeneity, treatment heterogeneity and the inclusion of immature studies. Further analyses⁷¹ have continued to conclude that the benefits of MAB are modest. It appears that they comprise an approximate 2% improvement in overall survival. Other studies have however suggested larger advantages to non-steroidal anti-androgens^{74, 75} and large advantages to nilutamide as the anti-androgen component of MAB.⁷²

These latter studies were based on published data only, whereas the PCTG was based on individual patient data from published and unpublished studies and based on an extensive search of several electronic databases as well as contact with individual researchers and with pharmaceutical companies. However the contention that non-steroidal anti-androgens may confer greater benefits was supported by the updated report from the PCTG which reported significant, though small, overall survival benefits when nilutamide and flutamide were used compared with the steroidal anti-androgen cyproterone acetate.⁷¹

Issues of trial design, data analysis and interpretation have been considered in a study which re-analysed the EORCT 30853 trial with a Cox proportional hazards regression model and allowed a different hazard ratio in the first time period (time 0 to 1.5 years after randomisation) and the second time period (year 1.5 onwards).⁷⁹ This was based on the assumption that in all previous studies the potential benefits from MAB would be reflected in a constant hazard ratio over time whereas this was unlikely to be the case. This study has concluded that the benefits from MAB are unlikely to be clinically relevant.

The relative efficacy of the different forms of anti-androgen therapy was analysed in a meta-analysis.⁵⁹ No significant differences were found between diethylstilbestrol (DES), orchidectomy or LHRH analogues, in terms of overall survival, progression free survival or time to failure. Although the differences between the observed hazard ratios for anti-androgen as monotherapy and orchidectomy, DES or LHRH analogues were not significant, the confidence limits of the meta-analysis were wide. Clinically important differences can not therefore be precluded by the review and have been seen in one primary study – a RCT comparing bicalutamide with orchidectomy in advanced disease.⁶¹ The systematic review conducted by researchers at the United States' Agency for Health Care Policy and Research came to similar conclusions, but also noted that there may be less effect on sexual function from non-steroidal anti-androgen monotherapy.⁶⁰ Although individual trials⁶⁵ suggest quality of life benefits, the conclusion from the AHRQ study was that there was insufficient data to make a firm statement about the effects of different forms of anti-androgen therapy on quality of life.

Conclusions

The weight of current evidence probably supports immediate rather than deferred hormone therapy in men with active, progressive disease, but this conclusion is tenuous and must be reviewed as more evidence accumulates.

The survival benefits of maximum androgen blockade compared with monotherapy appear to be of questionable clinical significance.

d) Second-line treatment

No randomised trials have established an optimum second line therapy for patients relapsing after first line hormone therapy. Although some patients will respond to second-line hormone therapy, many do not and they are considered to have hormone refractory prostate cancer (HRPC). The options for second-line therapy include corticosteroids, alternative anti-androgens, chemotherapy and other systemic agents. Anti-androgen withdrawal responses are clearly documented.⁸¹ A randomised trial comparing anti-androgen withdrawal alone to the replacement of anti-androgen therapy with ketoconazole has shown no overall survival differences but a higher response rate in patients receiving ketoconazole.⁸⁰ However, ketoconazole had substantial toxicity in this study.

Because of the overwhelming predominance of bone metastases palliative radiotherapy (either as EBRT or using bone-seeking radionuclides, such as Strontium-89) has been a major focus for study. There is good evidence that a single treatment with EBRT is as effective as more prolonged schedules for relieving an individual site of metastatic bone pain.^{84, 85} However, bone pain from metastatic prostate cancer is often multifocal and wide-field radiotherapy (e.g. hemibody radiotherapy) has also been studied. There is high quality evidence that Strontium-89 is effective in relieving metastatic bone pain,⁸²⁻⁸⁴ albeit at the expense of a degree of haematological toxicity.

In a systematic review of therapy with Strontium-89⁸² the results of four randomised trials were presented, but no meta-analysis was performed. In one trial, Strontium-89 was given alone or with EBRT; in one Strontium-89 was compared with palliative EBRT and in two trials Strontium-89 was compared with placebo. Two trials suggested that Strontium-89 treated patients developed significantly fewer new sites of pain compared with EBRT alone.⁸² In a further trial, 103 patients treated with intensive induction chemotherapy, were randomised to doxorubicin alone or doxorubicin and Strontium-89.⁸⁶ The results suggested improvements in time to progression in the strontium-treated patients. The results of a further randomised trial, the EORTC 30921 study, randomising patients between local field irradiation and Strontium-89, are expected shortly.

Chemotherapy was previously not considered effective for prostate cancer, on the basis of older phase I/II studies, in part owing to the difficulties in assessing objective response. There is high quality evidence that the combination of chemotherapy in the form of mitoxantrone and corticosteroids is of benefit in patients with HRPC. A randomised trial, conducted in Canada, had as its primary outcome a reduction in pain score and a subsequent analysis addressed other quality of life aspects.⁸⁸

A second randomised study suggested a small but significant improvement in surrogate outcomes of time to progression and PSA response, but no improvement in median survival or change in quality of life in combination with chemotherapy.⁸⁹ There were trends in favour of chemotherapy in terms of quality of life and several items in the quality of life measure related to pain.

A third randomised trial compared first-line orchidectomy alone with orchidectomy and mitomycin in 189 patients with metastatic prostate cancer and

poor prognostic features and found chemotherapy to be detrimental in terms of overall survival and of significant toxicity.⁹⁰

In general, these studies were performed in patients who had been heavily pre-treated, in whom palliation was the prime concern. More recently, there has been interest in chemotherapy studies in patients who were less heavily pre-treated, in whom response was considered a valid endpoint. It is important that survival and quality of life should be considered for this group of HRPC patients.

A systematic review of chemotherapy studies examined 52 trials comprising 2,028 patients, based on a comprehensive search strategy.⁸⁷ Four studies suggested improvements in pain scores, but there was wide variation in the time to progression and overall survival, indicating the heterogeneity of the patient population. It is not possible to determine the number of randomised trials in this study.⁸⁷ Systemic agents being tested in phase II and III studies include paclitaxel and estramustine phosphate,^{91, 92} ketoconazole^{80, 98} and other agents such as tyrosine kinase inhibitors.^{94, 95} Definite conclusions on their efficacy must await further, large scale studies.

The combination of a taxane given weekly with or without estramustine phosphate has been reported in randomised⁹² and non-randomised^{91, 93} phase II studies. In the randomised trial, conducted in a community-based oncology practice setting in the US, 166 patients with progressive HRPC and bone metastases were randomised between weekly paclitaxel alone or weekly paclitaxel and estramustine phosphate. Response rates (a 50% reduction in PSA) were superior in the combination arm (28% compared with 48%, $p = 0.01$) but there were no significant differences in time to progression or survival.⁹² Two other randomised trials comparing the combination of docetaxel (given weekly or two-weekly) and estramustine phosphate with mitoxantrone and prednisolone are currently in progress in the USA.

Bisphosphonates have been tested in several randomised studies. The PRO5 MRC double-blind trial randomised patients with bone metastases who were starting or already responding to androgen ablation therapy to sodium clodronate or placebo and has reported its first results.⁹⁶ Analysis indicates a non-significant trend in favour of adjuvant bisphosphonates in time to symptomatic progression and overall survival and further studies are required. The MRC PRO4 double-blind randomised trial of sodium clodronate in 504 patients with T2 to 4, M0 disease is to have its first analysis in 2003.

A randomised trial comparing ketoconazole alone compared with ketoconazole and aledronate in 62 patients showed no differences in PSA response.⁹⁸ A randomised trial of leuprolide alone or leuprolide and pamidronate, administered every 12 weeks intravenously in 47 patients with hormone-sensitive disease, suggests that bisphosphonates can preserve bone mineral density in hormone-treated patients.⁹⁹ A randomised controlled study, randomised 422 men with HRPC to zoledronate or placebo given three weekly for 15 months⁹⁷ and found a significant prolongation in the time to the first skeletal related event but no survival data were presented and some renal toxicity was observed.

Combinations of systemic palliative therapy are also under study. The NCI:C/MRC PR3/PR07 trial is shortly to complete, comparing mitoxantrone and prednisolone alone with mitoxantrone, prednisolone and sodium clodronate.

Several studies of novel biological therapeutic agents have also been conducted. In a randomised trial of 406 patients, all patients were treated with mitoxantrone and prednisolone and were randomised to one of three arms. Patients received the matrix metalloproteinase inhibitor prinomastat/AG3340 at 5mg or 10mg dose levels or a placebo drug taken orally twice daily.⁹⁴ The preliminary results indicate no differences in response rates, median progression-free survival or overall survival.

A randomised trial of the endothelin receptor antagonist atrasentan/ABT-627 randomised 288 patients with HRPC to 2.5mg or 10mg of the drug or to placebo once a day. The preliminary results showed a significant benefit in terms of time to clinical or PSA progression for the active drug; this was based on a treatment received rather than on the more conservative intent-to-treat analysis.⁹⁵ Further phase III studies with this agent are in development.

Conclusions

The optimum management of prostate cancer on relapse after a first hormone treatment is unclear. Some patients respond to second-line hormones, including corticosteroids. Other options include chemotherapy, bisphosphonates and biological agents which should be further evaluated in clinical trials. Palliative radiotherapy is effective for bone pain and can be administered as a single fraction in many patients or may be given in the form of Strontium-89.

Table 5.1a: The treatment of localised disease: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Duchesne, 2001. ³ Australia I / III	To evaluate the efficacy of radiotherapy for patients with localised prostate cancer.	<p><i>Participants</i> Patients with localised prostate cancer.</p> <p><i>Interventions</i> Radiotherapy, (external beam, conformal radiotherapy (CRT), dose escalation, intensity modulated radiotherapy (IMRT) and brachytherapy).</p> <p><i>Design</i> RCTs/large series.</p>	<p>Overall survival.</p> <p>Disease specific survival.</p> <p>Biochemical control/biochemical no evidence of disease (bNED).</p>	<p><i>Conformal treatment at conventional doses</i> 2 RCTs were located. Both demonstrated a reduction in acute toxicity when conformal radiotherapy was compared with conventional radiotherapy.</p> <p><i>Conventional treatment at various doses</i> No RCTs were located. A comparison with historical controls suggested a benefit to higher doses.</p> <p><i>Dose escalation - conformal treatment</i> Non-RCTs suggest improved rates of bNED for some patients with higher dose – up to 80Gy.</p> <p>One RCT reported preliminary results suggesting a bNED advantage to 78Gy, compared with 70Gy in patients with PSA levels greater than 10ng/ml but not in patients in 'good risk' or 'poor risk' groups.</p> <p>From non-randomised studies, the frequency of grade III urinary adverse effects was 7% to 9%. Impotence was seen in 31% to 50% of patients and grade III bowel morbidity was seen in 3% to 12%.</p> <p><i>Intensity modulated radiotherapy (IMRT)</i> Data on outcomes and on late morbidity are yet available.</p> <p>Acute morbidity appears to be comparable to conformal treatment.</p> <p><i>Brachytherapy using temporary high dose rate (HDR) implants</i> A matched comparison study from one centre suggests improved rates of bNED in patients treated with brachytherapy and external beam compared with external beam alone (67% compared with 44%) but higher urinary morbidity was seen in those patients treated with both modalities.</p> <p>Several phase I/II studies have been conducted using combined high dose rate (HDR) implants and radiotherapy but no definitive results were available to inform an estimate of the optimum regime.</p>	Search strategy and inclusion/exclusion criteria, not strictly for a 'systematic' review.	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> A MEDLINE search was conducted covering publications from 1996 to mid 2000. A search strategy was provided.</p> <p><i>Inclusion criteria</i> English language articles reporting series with a minimum follow-up of 2 years were included.</p> <p><i>Quality assessment</i> Yes</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of the results</i> Yes – A narrative synthesis was presented.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Frodin, 1996. ⁴ Sweden I / III	To determine the value of radiotherapy compared with surgery in the treatment of all grades of prostate cancer.	<p><i>Participants</i> Patients undergoing radiotherapy for the treatment of all grades of clinically confirmed prostate cancer.</p> <p><i>Interventions</i> Radiotherapy and brachytherapy were compared with prostatectomy.</p> <p><i>Design</i> RCTs and prospective and retrospective non-randomised studies were included.</p>	Overall survival. Disease-free survival. Local recurrence.	<p>53 reports were included. These detailed 4 RCTs, 3 prospective non-randomised studies and 44 retrospective studies. A total of 52,005 patients were included in these studies.</p> <p>Microscopic tumour growth and/or non-palpable local recurrence rates ranged from 0% to 20% for patients treated with radiotherapy and from 0% to 9% for those who underwent surgery.</p> <p>In patients with a small palpable tumour, overall survival ranged from 67% to 93% at 5 years and 20% to 70% at 10 years for those treated with radiotherapy and from 74% to 94% at 5 years and 42% to 78% at 10 years for those who underwent surgery.</p> <p>Rates of disease-free survival ranged from 38% to 90% at 5 years and 20% to 85% at 10 years for those treated with radiotherapy. Rates of local recurrence ranged from 0% to 23%. These data were not well reported in the series reporting the outcomes of surgery.</p> <p>In patients with palpable tumour extending into or through the capsule, overall survival at 5 years ranged from 40% to 90%. Disease-free survival at 5 years was reported to range from 20% to 46%. At 15 years, overall survival ranged from 18% to 27% while disease-free survival was 40%. Local recurrence rates for these patients were 12%, 19% and 25% at 5, 10 and 15 years respectively.</p> <p>In patients with tumour invasion of adjacent structures, overall survival ranged from 10% to 51% at 5 years and from 17% to 36% at 10 years. The frequency of local recurrence was found to range from 19% to 40% and was therefore higher than for T3 cancer.</p>	<p>A wider ranging search strategy may have increased the scope of the review.</p> <p>While MEDLINE is a large database, it has an English language bias and a bias towards publications originating in North America.</p> <p>Further information on toxicity, side effects etc may have been a useful addition.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE was searched to 1993. A search strategy was provided.</p> <p><i>Inclusion criteria</i> RCTs assessing the use of radiotherapy among patients with prostate cancer T1 to T4 were included.</p> <p><i>Quality assessment</i> was by an independent review of identified articles.</p> <p>The SBU recommendations system was used to evaluate studies, which a) classifies reports by type of study and b) assesses the scientific quality and 'weight of the evidence'.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Selley, 1997. ¹ UK I / III	<p>To determine the consistency of systematic reviews relating to the acute care, diagnostics, imaging, methodology, pharmaceuticals, population screening and primary and community care of early localised prostate cancer.</p> <p>To provide an overview to enhance the knowledge base and form the basis for future decisions in this field.</p>	<p><i>Participants</i> Men with localised prostate cancer</p> <p><i>Interventions</i> Radical prostatectomy, radical radiotherapy and conservative management.</p> <p><i>Design</i> RCTs, retrospective and prospective observational studies.</p>		<p>Available evidence for the effectiveness of treatments for localised prostate cancer was found to be inconclusive.</p> <p>Cancer specific survival rates are approximately 60% following radical radiotherapy, 80% following conservative management and 90% following radical prostatectomy.</p> <p>(10% difference between radical and conservative treatment)</p> <p>Informed patient choice is an essential component of treatment decisions.</p>	<p>A comprehensive and well-structured review.</p> <p>A thorough search strategy was presented and searched MEDLINE, EMBASE, Cancerlit, Social Science Citation Index, Science Citation Index, PsycLIT, DHSS Data, Applied Social Sciences Indexes and Abstracts (ASSIA) from 1990 to 1995.</p> <p>Data were obtained from studies on economic evaluation which were located from searches from 1986 owing to scarcity of evidence.</p> <p>Further investigation of short- and medium-term outcomes, quality of life and patient information are required.</p> <p>RCTs and observational studies were analysed together owing to lack of available good quality evidence.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> Yes</p> <p><i>Search strategy</i> Yes</p> <p><i>Inclusion criteria</i> Selection criteria were tailored to each sub-section of the review.</p> <p>A focus on early prostate cancer was maintained.</p> <p>Studies with populations of greater than 100 patients were preferred but those of greater than 50 patients were accepted.</p> <p>Primary research data were included in the report.</p> <p>Retrospective and prospective studies were included.</p> <p><i>Quality assessment</i> Appropriate control and comparison groups were studied using suitable outcome measures, which were assessed in a blind manner.</p> <p><i>Study details</i> Yes</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
<i>Section 1</i>						
	To determine the suitability of conservative management for men with localised disease and its effectiveness compared with more radical treatments.	<p><i>Participants</i> Men with localised prostate cancer.</p> <p><i>Interventions</i> Conservative management</p> <p><i>Design</i> 1 RCT and 10 observational studies of both retrospective and prospective designs.</p>	<p>Survival.</p> <p>Progression free survival.</p> <p>Disease progression.</p> <p>Mortality.</p> <p>Quality of life.</p>	<p>11 Studies including 1 RCT, 2 observational studies, 5 retrospective observational studies and 3 prospective observational studies. In addition two studies reported pooled results from 6 of the primary studies. A total 1,419 patients were included in this review.</p> <p><i>Effectiveness</i> Intercurrent death rates range from 20% to 47% in patients with a mean age ranging from 67 years to 86 years.</p> <p>Relatively low prostate cancer specific death rate for men receiving conservative management.</p> <p>Rates of local progression for confined disease range were from 35% to 70%.</p> <p>Rates of progression to metastases were from 10% to 15%.</p> <p>In patients managed conservatively following early detection of prostate cancer, 8.5% to 10% of patients had locally or systematically progressive disease after 10 years of follow-up.</p> <p>In patients with low grade tumours, the risk of progression or metastases was less than 50%.</p>	1 RCT and additional lower grade studies were combined.	

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Section 2						
	To determine whether radical prostatectomy in men with localised tumours reduces mortality from prostate cancer.	<p><i>Participants</i> Men with localised prostate cancer.</p> <p><i>Interventions</i> Radical prostatectomy (including nerve sparing, retropubic and perineal techniques) and pelvic lymph node dissection.</p> <p><i>Design</i> RCTs and observational studies.</p>	<p>Overall survival.</p> <p>Cause specific survival.</p> <p>Progression-free survival.</p> <p>Metastasis-free survival.</p> <p>Recurrence-free survival.</p> <p>Extra-capsular extension.</p> <p>Progression.</p> <p>Treatment complication rate.</p> <p>Mortality.</p> <p>Blood loss.</p> <p>Sexual function.</p> <p>Incontinence.</p> <p>Quality of life.</p>	<p>There is a lack of high quality data from RCTs on survival following radical prostatectomy. Evidence about radical prostatectomy is largely based on retrospective observations of series of men followed-up for varying periods. None of these were performed in the UK.</p> <p>2 RCTs and 15 retrospective observational studies were found (total n = 5,410).</p> <p>At 10 years following radical prostatectomy, the cause specific survival was between 86% and 91% and the rate of freedom from clinical evidence of disease ranged from 57% to 83%.</p> <p>Early complication rates ranged from 7% to 16% (up to 30 days) and late complication rates (post 30 days) from 1% to 14%.</p> <p>Treatment complications commonly reported included operative and post operative mortality (0.2% to 1.2%), blood loss (varying between 100 to 2,000ml), deterioration of sexual function (51% to 61%) and incontinence (ranging from 4% to 21% for mild or stress incontinence and from 0% to 7% for total incontinence).</p> <p>The risk of complications increased with age, particularly for those over 75 years.</p> <p>The expected benefits of surgery decreased with increasing age, with only men aged 60 to 65 years likely to achieve benefit.</p> <p>The quality adjusted life expectancy decreased for men 70 years and over.</p> <p>Approximately 30% of patients experienced raised PSA levels of greater than 40ng/ml postoperatively.</p>	<p>A comprehensive and well-structured review.</p> <p>RCTs and retrospective studies were combined.</p> <p>The overall benefits of radical surgery remain inconclusive owing to the absence of high quality evidence.</p>	

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
	Section 3					
	<p>To determine the most effective and appropriate radiotherapy techniques.</p> <p>To define the optimal selection of patients for treatment.</p> <p>To assess the use of radiotherapy compared with other treatment modalities for men with prostate cancer.</p>	<p><i>Participants</i> Men with localised prostate cancer.</p> <p><i>Interventions</i> Radiotherapy - external beam radiotherapy (EBRT) and radioactive seed implant (brachytherapy).</p> <p><i>Design</i> RCTs and observational studies.</p>	<p>Survival rates.</p> <p>Disease-free survival.</p> <p>Recurrence rates.</p> <p>Progression rates.</p> <p>Complication rates.</p>	<p>21 observational studies and one RCT were located (total n = 6,042 patients). The majority of studies of outcomes following radiotherapy are observational in design, making comparisons between studies difficult. Overall, it appears that survival and recurrence rates following radiotherapy are strongly related to grade and stage of disease.</p> <p>Five year survival for patients with T1 or T2 disease averaged at from 70% to 80%.</p> <p>Local and distant recurrence increased with higher tumour stage and lower differentiation. The development of metastases is significantly greater for higher stage disease.</p> <p>Local progression was seen in from 10% to 20% of patients with T1 and T2 disease while progression to metastases was seen in 20% to 40% of such patients.</p> <p><i>Radioactive seed implants and conformal radiotherapy</i> Survival was related to disease grade and stage with similar survival rates to the rates seen in external beam radiotherapy.</p> <p>High rates of post treatment complications have been reported.</p> <p>The reported incidence of complications for radiotherapy ranged from 15% to 94%. Acute complications included rectal bleeding, cystitis, diarrhoea, proctitis, haematuria and skin reactions (see comments).</p> <p>Impotence within 6 months of treatment was found in 25% to 40% of patients.</p> <p>Late complications, occur more than 3 months after treatment, included urethral and recto-anal strictures, rectal and bladder ulceration, chronic cystitis, urinary incontinence and impotence.</p>	<p>Very few good quality RCTs were available.</p> <p>The observational data was found to carry many methodological flaws.</p> <p>European data and in particular UK data, are required to supplement this information. Some additional RCTs have been published since this review has been completed.</p> <p>RCTs and observational/outcome studies were combined owing to lack of good quality evidence available.</p> <p>Some studies reported all acute complications while others report only severe complications.</p> <p>The majority of patients will experience some form of acute complications. Therefore studies which report all complications may provide high/misleading rates.</p>	

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Chamberlain, 1997. ² UK III	To prepare a systematic review of the demands which all phases of the management of prostate cancer may have on the NHS in England and Wales.	<p><i>Participants</i> Men with prostate cancer.</p> <p><i>Interventions</i> All stages of prostate cancer management.</p> <p><i>Design</i> No details on the design of included studies are given.</p>	<p>Burden of prostate cancer on health (Incidence, mortality).</p> <p>Burden of prostate cancer on health service.</p> <p>Pathogenesis and natural history.</p> <p>PSA measurement.</p> <p>Screening for prostate cancer DRE, TRUS, PSA).</p> <p>Diagnosis.</p> <p>Treatment of localised prostate cancer.</p> <p>Treatment for advanced prostate cancer.</p>	<p>Only results relevant to treatment are presented here.</p> <p><i>Treatment</i> The comparative effectiveness of active monitoring, radical prostatectomy and radical radiotherapy is unknown and results from 4 international trials will not be available for some years. The review recommends that active monitoring (reduced incidence of side-effects) be offered to men with less than 10 years life expectancy, T1a tumours and a Gleason grade of less than 4. It recommends that prostatectomy be performed by trained urologists and complications should be audited. Similar considerations should apply to men referred to radical radiotherapy. General surgeons and urologists should recruit patients into the UK MRC PRO6 trial prior to referral to a specialist.</p> <p><i>Hormone therapy</i> Androgen deprivation (surgical or medical castration, using LHRH analogues) is standard treatment for locally advanced and metastatic cancer. Evidence suggests that immediate rather than deferred androgen deprivation delays disease progression. No significant improvement was seen in survival when anti-androgens were combined with castration. Hormone-refractory disease requires palliation with surgery, radiotherapy and analgesics.</p> <p>The review recommends that patients be offered maximum androgen blockade, but only in a randomised trial setting. More data are required on quality of life and treatment costs issues.</p>	<p>No search strategy was provided and the review was not comprehensive.</p> <p>Although cost implications to NHS were considered, indirect costs to the patient were unavailable.</p> <p>No projected costs of recommendations.</p> <p>Some of the information presented originated from discussion with specialists.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> None given</p> <p><i>Quality assessment</i> No</p> <p><i>Appropriate synthesis of results</i> No formal analysis performed.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Conseil d'Evaluation des Technologies de la Sante du Quebec, 2000. ²⁴ Canada III	To determine outcomes of brachytherapy and compare these to other treatment modalities.	<p><i>Participants</i> Patients undergoing brachytherapy for the treatment of confirmed prostate cancer.</p> <p><i>Interventions</i> Brachytherapy.</p> <p><i>Design</i> Published reports of brachytherapy. Retrospective studies.</p>	<p>Recurrence-free survival.</p> <p>Biochemical failure.</p> <p>Complication rates.</p>	<p>33 studies, 6,860 patients.</p> <p><i>Mean 7 year recurrence-free survival</i> Radical prostatectomy 84% Brachytherapy 79%</p> <p><i>Freedom from biochemical failure</i> Men with low pre-treatment PSA – 74% to 98% Men with high pre-treatment PSA – 80%</p> <p>Negative biopsy rates range from 80% to 55% at one year (increasing with longer follow-up).</p> <p><i>Complications</i> Impotence rates range from 0% to 34%.</p> <p>1% of men who had not previously undergone transurethral resection of the prostate (TURP) and 12.5% of men who had undergone TURP previously experienced incontinence.</p> <p>Reported side effects were substantially less frequent with brachytherapy than either surgery or EBRT.</p>	<p>No RCTs comparing brachytherapy to other treatments were identified.</p> <p>Searching a broader range of databases may have improved the study methodology.</p> <p>The North American bias of the database may have introduced geographic publication bias.</p> <p>Good quality assessment criteria were utilised, based on the specific aims of the review question.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE was searched from 1972 to 1999. Reference lists of located publications were searched. No search strategy was provided however.</p> <p><i>Inclusion criteria</i> Studies assessing the use of brachytherapy and brachytherapy compared with other treatments for patients with prostate cancer were included.</p> <p><i>Quality assessment</i> Studies were independently assessed and ranked using standardised criteria.</p> <p><i>Study details</i> Detailed information tables were provided.</p> <p><i>Appropriate synthesis of results</i> Yes</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods						
<p>Crook, 2001.²³ Canada III</p>	<p>To examine the role of brachytherapy in treating clinically localised prostate cancer.</p>	<p><i>Participants</i> The series was limited to patients with Stage T1 and T2 prostate cancer.</p> <p>Brachytherapy was performed under ultrasound or CT guidance.</p> <p><i>Interventions</i> Brachytherapy alone or with external beam radiotherapy.</p> <p><i>Design</i> 10 case series and 1 cohort study was located of brachytherapy alone.</p> <p>1 case series of external beam radiotherapy and brachytherapy in combination was located.</p> <p>2 cohort studies of external beam and brachytherapy compared with brachytherapy alone were located.</p>	<p>Biochemical failure (bNED).</p> <p>Biopsy results.</p> <p>Toxicity.</p>	<p>16 studies.</p> <p><i>Brachytherapy alone</i> A wide variation was seen in 5 year bNED rates owing to differences in patient selection criteria; the overall (for patients with any grade of tumour) rates varied from 63% to 93%.</p> <table border="0" data-bbox="965 454 1400 534"> <tr> <td>5 year bNED - Gleason 2 to 4</td> <td>86%</td> </tr> <tr> <td>Gleason 5 to 6</td> <td>63%</td> </tr> <tr> <td>Gleason 7 to 10</td> <td>32%</td> </tr> </table> <p>Comparison of the rates of positive biopsies was difficult. Rates varied from 3% to 26% at median times of 6 months to 69 months.</p> <p>Acute adverse effects – irritative urinary symptoms (grade 1 to 2) were found in 46% to 54% of patients overall, 29% of patients at 12 months and 14% of patients at 24 months.</p> <p>Acute retention was seen in 1% to 14% of patients and acute proctitis was seen in 1% to 2% of patients.</p> <p>Chronic adverse effects – incontinence was seen in 5% to 6% of patients. Haematuria was seen in 1% to 2% of patients. Strictures were seen in 1% to 2% of patients. Proctitis was seen in 1% to 3% of patients and impotence was seen in 4% to 14% of patients.</p> <p><i>External beam radiotherapy followed by brachytherapy</i> bNED 60% to 79%, cNED 63%</p> <p>In two non-randomised but controlled studies, both biochemical and clinical NED status was achieved more commonly in those men who received all of their radiotherapy using brachytherapy techniques alone.</p> <p>Chronic adverse effects were not well described. In one study, 23% of men suffered impotence.</p> <p><i>Brachytherapy followed by external beam radiotherapy</i> Positive biopsies were seen in 48% of patients in one study.</p> <p>Adverse effects were reported in one study. 6% of patients suffered, recto-vesical fistulae, 3% suffered an anal ulcer, 16% suffered haemorrhagic proctitis and 25% suffered severe persistent cystitis.</p>	5 year bNED - Gleason 2 to 4	86%	Gleason 5 to 6	63%	Gleason 7 to 10	32%	<p>Strategy could have been broader – did not include abstracts.</p> <p>Urinary toxicity may relate to older dosimetric technique.</p>	<p>The investigators were contacted for further methodological information.</p> <p><i>Review question</i> Yes</p> <p><i>Literature search</i> An electronic search of MEDLINE and Cancerlit was conducted covering the period from 1998 to April, 1999.</p> <p><i>Inclusion and exclusion criteria</i> Yes</p> <p><i>Quality assessment</i> Yes</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes</p>
5 year bNED - Gleason 2 to 4	86%											
Gleason 5 to 6	63%											
Gleason 7 to 10	32%											

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Goluboff, 1996. ¹⁴ USA III	To assess the results of surgery compared with external beam radiotherapy (EBRT) in localised prostate cancer with particular reference to PSA levels as the most relevant surrogate end-point.	<p><i>Participants</i> Patients with localised prostate cancer.</p> <p><i>Interventions</i> EBRT or radical surgery with mean follow-up of at least 1 year and with measurement of post-treatment PSA levels in at least some patients.</p> <p><i>Design</i> Retrospective series.</p>	The achievement of bNED in the short term (< 5 years) and the long-term (5, 10 and 15 years).	<p><i>Short-term control (mean follow-up 12 to 48 months)</i> EBRT, 8 studies, n = 1,697. Surgery, 4 studies, n = 1,604. Percentage of cases with PSA levels < 10ng/ml was found to be lower in those patients treated surgically than in those treated by EBRT. However, overall biochemical recurrence rates were stated to be 'similar' between EBRT and surgery.</p> <p><i>Long-term control (mean follow-up 34 to 162 months)</i> EBRT, 9 studies, n = 1,382. Surgery, 4 studies, n = 5,339. bNED rates were lower following EBRT than following surgery. Five year bNED rates ranged from 24% to 60% for those treated by EBRT and from 69% to 83% for those treated by surgery. Ten year bNED rates ranged from 20% to 40% for those treated by EBRT and from 47% to 70% for those who underwent surgery. Fifteen year bNED rates ranged from 19% to 46% in those treated by EBRT and from 40% to 75% for those treated by surgery. Where follow-up was of less than 5 years duration, PSA-based recurrence rates were similar for EBRT and radical surgery. 10 and 15 year bNED rates are significantly lower in EBRT patients.</p>	<p>Definition of 'success' (bNED) may have been decided retrospectively in the EBRT studies owing to the variation in PSA levels.</p> <p>Clinical recurrence and survival were not considered. In one study those cases having died of prostate cancer or having recurrent disease (29%) were excluded.</p> <p>Owing to a lack of large RCTs relative efficacy is difficult to determine.</p> <p>Definition of short-term and long-term not reflected in the mean follow-up of individual patients series. Only 2 surgical series report 15 year NED and only 3 10-year bNED.</p> <p>No attempt was made to account for the selection bias which may have existed, possibly leading to case-mix effects in favour of the surgical treatment modality.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE search from 1990 to present (published Nov 1996) Search terms: prostate cancer; prostatectomy; radiation therapy.</p> <p><i>Inclusion criteria</i> Studies of external beam radiation therapy or radical surgery in patients with localised prostate cancer.</p> <p><i>Quality assessment</i> None provided</p> <p><i>Study details</i> Brief details</p> <p><i>Appropriate synthesis of results</i> Yes</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Merrick, 2001. ²⁵ USA III	To summarise the prostate brachytherapy literature and provide a comparative analysis of brachytherapy, radical radiotherapy and external beam radiotherapy outcomes for early stage carcinoma prostate.	<p><i>Participants</i> Patients with early stage cancer of the prostate.</p> <p><i>Interventions</i> Prostate brachytherapy, external beam radiotherapy and radical surgery.</p> <p><i>Design</i> Review of published studies.</p>	Biochemical evidence of disease. Toxicity data including urinary morbidity, rectal morbidity and erectile dysfunction.	<p><i>Efficacy</i> For patients with low-risk features, the biochemical results of prostate brachytherapy are as favourable as the most positive radical prostatectomy and external-beam radiation therapy series. In most studies, patients with intermediate- and high-risk disease have more durable biochemical outcomes when treated with brachytherapy (with or without external-beam radiation therapy). Multiple postoperative dosimetric studies supported the ability of brachytherapists to adequately encompass the target volume.</p> <p><i>Toxicity</i> Long-term urinary morbidity is primarily restricted to patients with a history of transurethral resection. Significant bowel dysfunction is uncommon. Although erectile dysfunction occurs in approximately 50% of patients at 5 years, 80% respond favorably to sildenafil.</p>		<p><i>Review question</i> Yes</p> <p><i>Literature search</i> While a search of MEDLINE was conducted, no search strategy or search dates were given.</p> <p><i>Inclusion criteria</i> No details were given.</p> <p><i>Quality assessment</i> None provided</p> <p><i>Study details</i> Brief details</p> <p><i>Appropriate synthesis of results</i> With the limited details it is not possible to assess the validity of the narrative synthesis conducted.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Vicini, 1999. ¹² USA III	To determine whether an optimal method of implantation for brachytherapy can be identified. To compare techniques currently in use.	<i>Participants</i> Patients with localised prostate cancer. <i>Intervention</i> Implants with or without external beam radiotherapy. <i>Design</i> Little information was presented about the design of research studies included.	Biochemical control.	16 studies calculated treatment outcomes based on pre-treatment PSA and biochemical control. 9 of these used permanent seed implants alone and 7 combined external beam radiotherapy with either permanent or temporary implants. The rates of biochemical control stratified for pre-treatment PSA were variable. At 3 to 5 years, the rates of biochemical control were as follows:- Less than 4ng/ml 48% to 100% 4 to 10ng/ml 55% to 90% 10 to 20ng/ml/ml 30% to 89% > 20ng/ml < 10%to 100% (PSA levels at pre-treatment.) Owing to substantial differences in reporting and distribution of prognostic factors, follow-up and the variable definitions of outcome, no inferential methodologies could be applied to data to determine optimum implant techniques.	The review was based on a search of only one database. Only the most recent studies with the largest groups of patients were put forward for analysis. Little information was included on study designs of the included studies. It is not possible to assess the quality of those included. The definition of biochemical failure varied from study to study and included > 4ng/ml, 2 PSA increases after nadir, 2 consecutive PSA rises, 2 consecutive PSA rises, single rise > 2ng/ml, nadir > 0.5ng/ml, PSA > 1ng/ml at follow-up	<i>Review question</i> Yes <i>Literature search</i> MEDLINE was searched (Jan 1985 to Aug 1998). English language articles were retrieved. <i>Inclusion criteria</i> Studies had to stratify patients by pre-treatment PSA and evaluate outcome using biochemical control as an endpoint. <i>Quality assessment</i> No details <i>Study details</i> Yes <i>Appropriate synthesis of results</i> Yes

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods								
Vicini, 1998. ⁵ USA III	To determine if the optimal radiotherapeutic management of prostate cancer can be determined when PSA levels are used to stratify patients and evaluate outcome.	<p><i>Participants</i> Patients undergoing radiotherapy for the treatment of prostate cancer.</p> <p><i>Intervention</i> Radiotherapy</p> <p><i>Design</i> Not stated</p>	Biochemical control (bNED).	<p>20 studies were retrieved. 4 studies detailed external beam radiotherapy, 8 detailed conformal radiotherapy and 8 detailed brachytherapy.)</p> <p>At 3 to 5 years, the rates of biochemical control were as follows:-</p> <table border="0"> <tr> <td>Less than 4ng/ml</td> <td>48% to 100%</td> </tr> <tr> <td>4 to 10ng/ml</td> <td>44% to 90%</td> </tr> <tr> <td>10 to 20ng/ml</td> <td>27% to 89%</td> </tr> <tr> <td>> 20ng/ml</td> <td>14% to 89%</td> </tr> </table> <p>(PSA levels at pre-treatment)</p> <p>Median Gleason score, T stage, definition of Biochemical control and follow-up were significantly different from series to series.</p>	Less than 4ng/ml	48% to 100%	4 to 10ng/ml	44% to 90%	10 to 20ng/ml	27% to 89%	> 20ng/ml	14% to 89%	A limited search strategy and no quality assessment criteria were presented.	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE was searched from 1986 to 1997. A search strategy was provided.</p> <p><i>Inclusion criteria</i> Pre-treatment PSA values were recorded and grouped for subsequent evaluation; post treatment PSA values were continuously monitored after treatment.</p> <p>Definitions of biochemical control used to evaluate outcome were stated; median follow-up was given.</p> <p><i>Quality assessment</i> Not stated</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes</p>
Less than 4ng/ml	48% to 100%													
4 to 10ng/ml	44% to 90%													
10 to 20ng/ml	27% to 89%													
> 20ng/ml	14% to 89%													

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Wills, 1999. ²⁶ Canada III	To determine if brachytherapy is an effective treatment in patients with prostate cancer.	<p><i>Participant</i> Patients with localised prostate cancer.</p> <p><i>Interventions</i> Brachytherapy with or without prostatectomy and/or external beam radiotherapy.</p> <p><i>Design</i> Prospective and retrospective studies were reviewed.</p> <p>Studies reporting patient outcomes following brachytherapy and those providing comparisons with other therapeutic options were included.</p>	<p>Recurrence (biochemical control).</p> <p>Recurrence (clinical control).</p> <p>Overall survival.</p> <p>Complication rates.</p>	<p>23 studies, with approximately 6,351 patients, were included.</p> <p><i>Recurrence (biochemical control)</i> Biochemical control rates ranged from 95% to 60% with ten year follow-up.</p> <p><i>Recurrence (clinical control)</i> Ranged from 5% to 35% through positive biopsies (depending on study protocol and time to follow-up).</p> <p><i>Overall survival</i> Ranged from 65% to no reported deaths.</p> <p>Disease specific deaths from prostate cancer ranges from 0% to 3%.</p> <p><i>Complication rates</i> Overall complications included mild acute urethritis and proctitis.</p> <p>Long-term complications were similar or lower than experienced with EBRT or RP.</p> <p>Incontinence (where reported) was 6% or less through all treatment modalities.</p> <p>Impotence ranged from 5% to 38%.</p> <p>Impotence was found to be present in 5% to 23% of patients who underwent brachytherapy with or without external beam radiotherapy.</p> <p>Most long-term gastrointestinal morbidity was less than 5% through all treatment modalities.</p> <p>Only one constituent study compared two treatment modalities. There was marginally less long-term urinary toxicity for conformal radiotherapy (CRT) than for brachytherapy. There was similar gastrointestinal toxicity and higher levels of impotence with CRT.</p>	<p>Comprehensive search strategy covering all the major databases. (Short timescale used owing to previous report covering earlier literature.)</p> <p>Absence of available controlled trials.</p> <p>Methodological quality of included studies evaluated as 'poor'.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> Cochrane Library, MEDLINE, Cancerlit, EMBASE and Cinahl were searched from 1997 to 1999. A search strategy provided.</p> <p><i>Inclusion criteria</i> Yes</p> <p><i>Quality assessment</i> Each study assessed and data extracted independently.</p> <p><i>Study details</i> Yes (Complete data extraction tables included in appendix).</p> <p><i>Appropriate synthesis of results</i> Yes</p>

Table 5.1b: The treatment of localised disease: primary studies

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Benoit, 2000. ¹⁹ USA VI	To report complications after prostate brachytherapy in a population based cohort.	<i>Participants</i> All men in the Medicare population who underwent prostate brachytherapy in 1991. <i>Interventions</i> Prostate brachytherapy. <i>Design</i> Retrospective.	Bladder outlet obstruction. Urinary incontinence. Erectile dysfunction.	2,124 men were identified. Minimum and maximum follow-up times were 24 months and 36 months. Complication rates were found to be as follows:- 8.3% Surgery for bladder outlet obstruction. 0.2% Artificial urinary sphincter 6.6% Transurethral resection of prostatic urethra 0.8% Transurethral resection of bladder neck 0.3% Transurethral incision of prostate 0.6% Balloon dilation 8.4% Erectile dysfunction diagnosed 0.3% Colostomy for radiation damage 2.2% Radiation colitis 1.8% Rectal fistula 1.1% Rectal ulcer	The Medicare database was accessed to identify all men in the Medicare population who underwent prostate brachytherapy in 1991. All subsequent Medicare claims identified for those patients undergoing treatment for possible complications.	<i>Sample</i> Pass <i>Inclusion/exclusion criteria</i> Pass <i>Entry point</i> Pass <i>Follow up</i> Pass <i>Outcomes</i> Pass <i>Sub series</i> N/A
Grimm, 2001. ²¹ USA VI	To report the 10-year biochemical outcome in early stage prostate cancer patients treated with Iodine-125 brachytherapy.	<i>Participants</i> 125 patients newly diagnosed prostate carcinoma Stage T1 to T2b <i>Interventions</i> Iodine-125 brachytherapy as sole therapy. The procedure was planned with ultrasound-guidance. Preloaded needles employing permanent Iodine-125 sources were used in each case. <i>Design</i> 10 year results of a cohort study of consecutive patients in one centre.	<i>Biochemical outcomes</i> PSA progression failure (2 consecutive rises in PSA). Time to failure. PSA response. <i>Clinical Outcomes</i> Local – positive biopsy or DRE. Distant – evidence of metastatic disease.	4 patients were classified as having developed local failure (positive biopsy) and 4 as having developed distant failure (as diagnosed following a positive bone scan). These 8 patients were classified as progressing by virtue of their PSA results and each recurrence occurred within 5 years of diagnosis. A further 8 patients were classified as having biochemical progression but without clinical evidence of disease. The total rate of biochemical failure was 16/125 patients (12.8%). The calculated freedom from biochemical failure rate was 85.1% (95% CI: 79.3% to 90.9%). No patients have died of prostate cancer.	Single institute study conducted over 3 years. Results indicate that the technique improved over the study period with later patients having an improved outcome. Monotherapy with Iodine-125 achieves high rate of biochemical and clinical control in low risk disease.	<i>Sample</i> Pass <i>Inclusion/exclusion criteria</i> Pass <i>Entry point</i> Pass <i>Follow up</i> Pass <i>Outcomes</i> Pass <i>Sub series</i> N/A
Lu-Yao, 1997. ²² USA	To determine overall survival and prostate	<i>Participants</i> 59,876 men registered with the SEER cancer registry who were aged 50 to 79 and who had	Prostate cancer specific survival. Overall survival.	59,876 men were included in the study. The mean follow-up was 44.5 months (and 10% of patients were followed up for 92 months or longer).	Large population-based study. The database was unable to account for other variables	Survival statistics were calculated using the Kaplan Maier method.

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods														
VI	cancer specific survival in men treated by prostatectomy, radiotherapy or conservative management.	<p>been diagnosed with clinically localised prostate cancer.</p> <p><i>Interventions</i> Prostatectomy. Radiotherapy. Conservative management.</p> <p><i>Design</i> Analysis of registry data.</p>	Relative survival.	<p>Radical prostatectomy was the most common treatment (n = 24,257). Of these 89% of patients underwent lymph node dissection, 51% had pathologically localised cancer and 80% underwent a complete radical prostatectomy.</p> <p><i>10 year prostate cancer specific survival</i> Grade 1 patients – 94% (95% CI: 91% to 95%) following prostatectomy; 90% (95% CI: 87% to 92%) following radiotherapy; 93% (95% CI: 91% to 94%) following conservative management.</p> <p>Grade 2 patients – 87% (95% CI: 85% to 89%) following prostatectomy; 76% (95% CI: 72% to 79%) following radiotherapy; 77% (95% CI: 74% to 80%) following conservative management.</p> <p>Grade 3 patients – 67% (95% CI: 62% to 71%) following prostatectomy; 53% (95% CI: 47% to 58%) following radiotherapy; 45% (95% CI: 40% to 51%) following conservative management.</p> <p>For patients who underwent prostatectomy, the 10 year prostate cancer specific survival rates were significantly higher by treatment received analysis then by intention to treat analysis (p < 0.0001).</p> <p>The tumour grade was significantly associated with reduced overall survival. When patients with grade 1 tumours were compared with age matched cohorts, they exhibited similar or better overall survival. When patients with grade 3 tumours were compared with similar groups, they exhibited much lower overall survival.</p> <p><i>Overall survival 5 years post diagnosis with grade 3 disease</i></p> <table border="0"> <tr> <td>Prostatectomy</td> <td>81%</td> </tr> <tr> <td>Radiotherapy</td> <td>70%</td> </tr> <tr> <td>Conservative management</td> <td>45%</td> </tr> </table> <p><i>Relative survival</i></p> <table border="0"> <tr> <td>Prostatectomy</td> <td>0.98</td> </tr> <tr> <td>Radiotherapy</td> <td>0.92</td> </tr> <tr> <td>Conservative management</td> <td>0.61</td> </tr> </table> <p><i>Prostate cancer specific survival</i></p> <table border="0"> <tr> <td>Prostatectomy</td> <td>87%</td> </tr> </table>	Prostatectomy	81%	Radiotherapy	70%	Conservative management	45%	Prostatectomy	0.98	Radiotherapy	0.92	Conservative management	0.61	Prostatectomy	87%	<p>such as PSA or T stage and as such the results do not adjust for bias in the allocation of patients to the treatments on a burden of disease basis.</p> <p>It was not possible to determine the factors which influenced the treatment decisions for particular patients.</p>	<p><i>Sample</i> Pass</p> <p><i>Inclusion/exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> Pass</p>
Prostatectomy	81%																			
Radiotherapy	70%																			
Conservative management	45%																			
Prostatectomy	0.98																			
Radiotherapy	0.92																			
Conservative management	0.61																			
Prostatectomy	87%																			

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
				Radiotherapy 86% Conservative management 69%		
Ragde, 2000. ²⁰ USA VI	To supplement an earlier report on brachytherapy, giving results to 12 year follow-up.	<p><i>Participants</i> Patients with T1 to T3 prostate carcinoma. No patients were treated with adjuvant hormone therapy.</p> <p>Patients at high risk of recurrence were allocated to Arm A and treated with brachytherapy alone. Those at low risk of recurrence were allocated to Arm B and were treated with both external beam radiotherapy (45Gy) and brachytherapy.</p> <p><i>Interventions</i> Transperineal prostate brachytherapy using Iodine-125.</p> <p><i>Design</i> Case series.</p>	PSA levels.	<p>229 patients were treated with Iodine-125 brachytherapy. The median follow-up was 122 months (18 to 144 months).</p> <p>The observed ten year survival rate was 70% for the whole series.</p> <p>The ten year disease-free survival rate was 66% for those low risk patients treated with brachytherapy alone.</p> <p>The ten year disease-free survival rate was 79% among high risk patients who were treated with both external beam radiotherapy and brachytherapy.</p> <p>75% of patients who experienced recurrent disease, recurred within 5 years of treatment.</p>		<p><i>Sample</i> Pass</p> <p><i>Inclusion/exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> Pass</p>

Table 5.2: Low-dose compared with high-dose external beam radiotherapy: RCTs

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Dearnaley, 2001. ³⁴ UK II	To determine the effect of dose-escalation and treatment margin in conformal radiotherapy of localised prostate cancer.	<p><i>Participants</i> Men with localised prostate cancer.</p> <p><i>Interventions</i> Standard dose conformal RT (64Gy) with (HD) or without (SD) 10Gy boost.</p> <p>Treatment margin of 1.0 cm (M1.0 group) or 1.5cm (M1.5 group).</p> <p><i>Design</i> RCT</p>	<p>Acute and late toxicity (RTOG).</p> <p>Biochemical control (PSA).</p>	<p>Median follow-up 3.5 years (range 0.6 to 5.2 years)</p> <p><i>PSA control</i> PSA levels were consistently less than 2ng/ml in 82%/69% of HD/SD groups (p = 0.06) and in 76% of patients whose operation involved a wide margin and 75% of those patients whose operations involved a narrow margin.</p> <p><i>Acute toxicity</i> No significant variation in bowel toxicity between groups was found.</p> <p>A higher frequency of bladder side effects was found among those patients whose operations involved a wider margin than in those with a narrow margin was found (p = 0.002) and among those patients in the high-dose group compared with those in the standard dose group (p = 0.006).</p> <p><i>Late toxicity</i> Bowel toxicity of greater than 2 on the RTOG scale was seen in 23%/11% of HD/SD groups respectively (p = 0.06) and 21% of patients whose operation involved a wide margin and 13% of those patients whose operations involved a narrow margin (p = 0.2).</p> <p>Bladder toxicity of greater than RTOG Grade 2 was seen in 18%/13% of HD/SD groups and in 21% of patients whose operation involved a wide margin and 10% of those patients whose operations involved a narrow margin.</p> <p>There was a similar impotence rate in all groups (59%).</p>	This report presents a small RCT; the results of the study may usefully be incorporated in a future systematic review.	<p><i>Randomisation</i> Yes.</p> <p>Allocation concealment Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>

Study Country Grade	Aims	Study design	<i>Outcomes</i>	Results	Comments	Methods				
Pollack, 2000. ³⁵ USA II	To determine the effect of radiotherapy dose on prostate cancer patient outcome.	<p><i>Participants</i> 305 patients with T1 to T3 Nx/N0 prostate cancer with a pre-treatment serum PSA analysis and no previous radiotherapy, prostatectomy or androgen ablation.</p> <p><i>Interventions</i> External beam radiotherapy with a 70Gy or 78Gy dose.</p> <p><i>Design</i> RCT.</p>	<p>bNED.</p> <p>Freedom from failure (FFF).</p> <p>5 year freedom from distant metastasis.</p> <p>Mortality.</p> <p>Overall survival.</p> <p>Overall 2 year biopsy positivity rate.</p>	<p><i>Freedom from biochemical and/or disease failure (FFF) at 5 years</i></p> <table border="0"> <tr> <td>70Gy group</td> <td>69%</td> </tr> <tr> <td>78Gy group</td> <td>79%, p = 0.058.</td> </tr> </table> <p>Pre treatment PSA, Gleason score and clinical stage were all found to be highly significant in single co-variate analysis.</p> <p>For patients with a pre-treatment PSA of less than 10ng/ml , the 5 year freedom from failure rate was approximately 80% for both treatment arms. For those with a pre-treatment PSA rate of greater than 10ng/ml , a significantly higher 5 year freedom from failure rate was seen in patients in the high dose arm (75% against 48%, p = 0.011).</p> <p>For patients with raised PSA levels and who had T1 or T2 disease, the HD arm was related to improved freedom from failure rates (90% against 60% at 5 years).</p> <p>For patients with raised PSA levels and who had T3 disease, the 78Gy arm was also related to improved freedom from failure rates (75% against 44% at 3 years; this was not statistically significant).</p> <p>For patients with raised PSA levels and who had histological score of Gleason grade 2 to 6, the 78Gy arm was again related to improved freedom from failure rates (91% against 56% at 4 years; this was not statistically significant). That the differences were non-significant may possibly be owing to small number of patients.</p> <p>5 year freedom from distant metastasis rates were similar for both treatment arms (95% to 98%). When stratified according to pre-treatment PSA levels, those with below 10ng/ml had a 98% to 100% rate of freedom from metastases at those with raised PSA levels (above 20 ng/ml) had a rate of 98% to 87%.</p> <p>The 5 year freedom from distant metastasis rate for the 78Gy group was 98%, while the 70Gy group saw an 87% rate (p = 0.54).</p>	70Gy group	69%	78Gy group	79%, p = 0.058.	<p>Preliminary results only were presented in this report. More mature data are expected to follow.</p> <p>4 patients were lost to follow-up.</p>	<p><i>Randomisation</i> Patients were randomised to receive either 70Gy or 78Gy of external beam radiotherapy.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes.</p> <p><i>Appropriate analysis of results</i> Intention to treat analysis used at randomisation.</p> <p>Survival curves were calculated from completion of radiotherapy using the Kaplan Meier and Berkson Gage methods.</p>
70Gy group	69%									
78Gy group	79%, p = 0.058.									

Table 5.3: The management of iatrogenic incontinence: systematic review

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Moore, 1999. ³⁸ UK III	To evaluate the effects of conservative (non-surgical) management for urinary incontinence after transurethral, suprapubic, radical retropubic or perineal prostatectomy.	<p><i>Participants</i> Men who had undergone a prostatectomy for either benign prostatic hyperplasia (BPH) or early prostate cancer.</p> <p><i>Interventions</i> Pelvic floor muscle training – ‘PFMT’. Biofeedback assisted PFMT. Electrical stimulation using a rectal electrode. TENS. A combination of the above methods.</p> <p><i>Design</i> Randomised and quasi-randomised studies.</p>	<p>Patient reported symptoms.</p> <p>Objective measures.</p> <p>Patient satisfaction.</p> <p>Health status measures.</p> <p>Quality of life.</p> <p>Impact of incontinence.</p> <p>Adverse events owing to treatment.</p> <p>Health economics economic analysis.</p>	<p>5 RCTs with a total of 365 patients were located.</p> <p><i>Pelvic floor muscle training compared with no active treatment</i> Two trials with a total of 141 patients. The results were inconsistent despite no significant heterogeneity between trials. A benefit is suggested particularly in the first few months after surgery. This conclusion may apply to quality of life measures.</p> <p><i>Pelvic floor muscle training and biofeedback compared with no active treatment</i> Two trials with a total of 79 patients were located. No conclusive results were found.</p> <p><i>PFMT and rectal electrical stimulation and biofeedback compared with no active treatment</i> One trial with 39 patients was located. At 3 to 6 months three of 20 patients in the intervention group were assessed as cured compared with one of 19 patients in the control group.</p>	<p>The study considers the majority of issues surrounding the topic area.</p> <p>A systematic approach to searching, study retrieval and quality assessment of included studies was adopted.</p> <p>The inconclusive outcome of this study is likely to have resulted from a lack of good quality RCTs available in this topic area.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> The Cochrane Incontinence Group Trials Register, MEDLINE, Cinahl, EMBASE, PsycLit and ERIC were searched up to January 1999. Researchers were contacted and conference proceedings searched. A search strategy was provided.</p> <p><i>Inclusion criteria</i> RCTs of conservative management of urinary incontinence after all types of prostatectomy (radical, transurethral and suprapubic prostatectomy). Men who underwent prostatectomy for either BPH or early stage prostate cancer</p> <p><i>Quality assessment</i> Selection bias and trial analysis bias. Random allocation in treatment order. None of the patients were blinded to treatment protocols.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes</p>

Table 5.4a: Morbidity of radical therapy for prostate cancer: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Robinson, 1996. ⁴¹ USA III	To determine rates of erectile dysfunction associated with external beam radiotherapy and radical prostatectomy.	<p><i>Participants</i> Men with confirmed early stage prostate cancer with known normal erectile functioning before treatment.</p> <p><i>Interventions</i> External beam radiotherapy and radical prostatectomy</p> <p><i>Design</i> Review of published studies and subsequent meta-analysis.</p>	Erectile function.	<p>40 studies were located with a total of 9,403 patients.</p> <p>A single logistic regression model used.</p> <p>The probability of maintaining normal erectile function after radiotherapy was 0.69 (95% CI: 0.661 to 0.709) and after prostatectomy was 0.42 (95% CI: 0.400 to 0.433) ($p < 0.0001$).</p> <p>These probabilities were calculated using the logistic regression co-efficient 0.780 (95% CI: 1.95 to 0.44).</p>	<p>This report constitutes a well structured and easily interpreted meta-analysis.</p> <p>No search strategy provided</p> <p>Various study limitations were considered.</p> <p>Data homogeneity was ensured by adhering to strict inclusion criteria and determining common definitions of erectile functioning and common assessment times.</p> <p>Methods used to collect data were not stated. This may affect reported levels of erectile dysfunction.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> The Alberta Health Knowledge Network, MEDLINE and Cancerlit were searched from 1970 to 1994. No search strategy was given.</p> <p><i>Inclusion criteria</i> No studies before 1970 were given.</p> <p>Studies providing results of external beam radiotherapy, radical prostatectomy and cryotherapy were included.</p> <p>Primary discrete data sets were required.</p> <p>Known pre-treatment sexual functioning status was required to be evident.</p> <p>Studies where patients were not receiving hormone therapy were included.</p> <p><i>Quality assessment</i> Papers reviewed to ensure certain variables were included.</p> <p>Only the most recent report was abstracted when one study was reported more than once to avoid duplication of data.</p> <p><i>Study details</i> Yes (Summary table of study information)</p> <p><i>Appropriate synthesis of results</i> Logistic regression model used.</p>

Table 5.4b: Morbidity of radical therapy for prostate cancer: primary studies

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods																		
Stanford, 2000. ⁴² USA VI	To determine changes in urinary and sexual function after radical prostatectomy in patients with clinically localised prostate cancer.	<p><i>Participants</i> 1,291 black, white and Hispanic men aged 39 to 79 years with clinically localised prostate cancer. Patients were accrued between October 1st 1994 and October 31st 1995. Mean age at diagnosis 62.9 years.</p> <p><i>Interventions</i> Radical prostatectomy as primary treatment within 6 months of diagnosis.</p> <p><i>Design</i> Retrospective population-based longitudinal cohort study.</p>	Dependent and independent variables relating to distribution and change in urinary and sexual function.	<p>Both sexual and urinary functions were age and race sensitive.</p> <p><i>Total urinary control</i></p> <table border="0"> <tr> <td>Baseline</td> <td>78.0%</td> </tr> <tr> <td>6 months</td> <td>20.5%</td> </tr> <tr> <td>24 months</td> <td>31.9%</td> </tr> </table> <p>Based on the composite score overall urinary function decreased from 91.2 at baseline to 75.1 at 24 months (p < 0.001). Men aged 75 to 79 years had the highest level of incontinence (13.8%.) following their operations.</p> <p><i>Impotence</i></p> <table border="0"> <tr> <td>Baseline</td> <td>5.0%</td> </tr> <tr> <td>6 months</td> <td>68.0%</td> </tr> <tr> <td>24 months</td> <td>44.2%</td> </tr> </table> <p>41.9% of patients reported that sexual performance was a moderate to large problem. Mean sexual function score decreased from 71.5% at baseline to 38.6% at 24 months (p < 0.001). Men of more than 60 years had a 61% risk of impotence after surgery compared with a 15.3% to 21.7% risk for younger patients (p < 0.001).</p> <p><i>Sexual function by race</i> (Reporting of firm erections at 24 months)</p> <table border="0"> <tr> <td>Black men</td> <td>38.4%</td> </tr> <tr> <td>White men</td> <td>21.3%</td> </tr> <tr> <td>Hispanic men</td> <td>25.9%</td> </tr> </table> <p>This difference was significant at the 0.001 level.</p> <p><i>Satisfaction with treatment</i> 4% of patients were dissatisfied at 24 months. 71.5% of patients stated they would make the same treatment choice again.</p>	Baseline	78.0%	6 months	20.5%	24 months	31.9%	Baseline	5.0%	6 months	68.0%	24 months	44.2%	Black men	38.4%	White men	21.3%	Hispanic men	25.9%	Eligible cases identified from the SEER registry and randomly <i>Sampled</i> to age and ethnicity strata. Self-administered questionnaires and an analysis of medical records were conducted 6 months after diagnosis, with a follow-up questionnaire at 24 months.	<p><i>Participants</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Reliability of interventions</i> Pass</p> <p><i>Comparability of groups</i> Pass</p> <p><i>Dose response established</i> N/A</p> <p><i>Objectivity of outcomes assessment</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Participant withdrawal</i> N/A</p>
Baseline	78.0%																							
6 months	20.5%																							
24 months	31.9%																							
Baseline	5.0%																							
6 months	68.0%																							
24 months	44.2%																							
Black men	38.4%																							
White men	21.3%																							
Hispanic men	25.9%																							

Table 5.5a: Hormone therapy in cancer of the prostate: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Bonney, 1998. ⁴⁸ USA I	To evaluate the benefits of neo-adjuvant hormone therapy prior to radical prostatectomy.	<p><i>Participants</i> Patients with clinically localised prostate cancer selected for treatment by radical prostatectomy.</p> <p><i>Intervention</i> Neo-adjuvant androgen ablation and radical prostatectomy compared with radical prostatectomy alone.</p> <p><i>Design</i> RCTs</p>	<p>Pathological (pT) stage.</p> <p>Tumour in surgical margin.</p>	<p>7 RCTs with a total of 1,354 patients were located. 1,283 patients could be evaluated for treatment effect and 1,274 for surgical margins.</p> <p><i>Surgical margin</i> Neo-adjuvant hormone therapy had a highly significant beneficial effect on the proportion of patients in whom surgical margins contained active disease ($p < 0.0001$).</p> <p><i>Treatment effect</i> The therapy had a highly significant beneficial effect on the pathological disease stage $p < 0.0001$.</p>	<p>A well structured meta-analysis of RCTs.</p> <p>Literature searching of more than one database may have increased the geographical and/or linguistic scope of the study.</p> <p>No search strategy provided.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> The MEDLINE database was searched to March 31 1997. No strategy provided.</p> <p>A review of published bibliographies was conducted.</p> <p><i>Inclusion criteria</i> RCTs comparing neo-adjuvant androgen ablation and radical prostatectomy compared with radical prostatectomy alone in localised prostate cancer.</p> <p><i>Quality assessment</i> Studies were assessed against standard and surgical end points.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes. Homogeneity, χ^2 distribution, risk ratios and confidence intervals calculated.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Roach, 2000. ⁴⁷ USA I	To assess the impact of short- and long-term androgen suppression on the disease specific and overall survival of men treated with radiotherapy for localised prostate cancer.	<p><i>Participants</i> Patients with clinically localised prostate cancer treated in one of five RTOG trials with radiotherapy alone.</p> <p><i>Intervention</i> Short- and long-term androgen suppression in patients undergoing radiotherapy.</p> <p><i>Design</i> Retrospective individual patient analysis of previously collected data for phase III randomised controlled studies included on the Radiotherapy and Oncology Group (RTOG) database.</p>	<p>Overall survival (OS).</p> <p>Disease specific survival (DSS).</p>	<p>Data from 5 RCTs were combined. Data from a total of 2,742 patients were included.</p> <p>Patients were retrospectively divided into four prognostic risk groups:</p> <p>Group 1: Gleason score 2 to 6 and T1 to 2 and N0;</p> <p>Group 2: Gleason Grade 2 to 6 and T3 and N0 or Gleason Grade 2 to 6 and N+ or Gleason Grade 7, T1 to T2 and N0;</p> <p>Group 3: T3 and N0, Gleason Grade 7 or Gleason Grade 7 and N+ or Gleason Grade 8 to 10 and T1 to 2 and N0;</p> <p>Group 4: T3 and N0, Gleason Grade 8 to 10 or Gleason Grade 8 to 10 and N+.</p> <p>Median pre-treatment PSA was 25ng/ml .</p> <p>Group 2 patients who received diethylstilbestrol or megestrol acetate significantly lower disease specific survival than those treated with radiotherapy alone (p = 0.0001).</p> <p>Patients treated with goserelin and flutamide had similar overall survival but better disease specific survival than all group 2 patients treated with radiotherapy alone (p = 0.003). Differences in survival became apparent in the Group 1 and 2 patients with 'bulky' disease who were treated according to the RTOG 86-10 protocol in both disease specific survival (p = 0.0001) and overall survival (p = 0.017).</p> <p>Group 3 and 4 patients who received long-term HT and RT in comparison with RT alone had significantly improved overall survival (p = 0.0003) and disease specific survival (p < 0.0001).</p> <p>Pre-treatment PSA levels greater than 20ng/ml were associated with an increased risk of distant metastasis (p = 0.002) and a need for salvage HT (p = 0.001) in patients treated with radiotherapy alone.</p> <p>Group 2 patients treated with radiotherapy alone with pre-treatment PSA greater than 100ng/ml had a survival rate</p>	<p>The report reported a detailed individual patient data analysis.</p> <p>Group 1 patients were not analysed owing to a lack of follow-up information or large trials.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> None applicable.</p> <p><i>Inclusion criteria</i> Consecutive prospective phase III RCTs assessing long- or short-term androgen suppression. Patients were included if they were evaluable and eligible and if follow-up information was available.</p> <p><i>Quality assessment</i> Limited information.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Cox proportional hazard models, Kaplan Meier actuarial estimates, Log rank tests and Median follow-up.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
				<p>which was statistically significantly lower than those with a PSA level of less than 100ng/ml (p = 0.009).</p> <p>Group 3 and 4 patients with a PSA level of more than 100ng/ml and treated with long-term hormonal therapy had a statistically significantly lower survival than those with a PSA of less than 100ng/ml (p = 0.002).</p> <p>A relationship between the duration of long-term HT and an associated improvement in survival was noted. Patients managed with HT for less than 2 years had a survival rate of 68%, those who had HT for between 2 and 5 years had a survival rate of 61% while those who had longer term HT had a survival rate of 83%.</p> <p>Taking HT for more than 5 years was associated with a significantly higher overall survival.</p> <p>The benefit experienced with the use of hormone therapy appeared to depend on the patient characteristics as well as the duration of treatment.</p>		

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Vicini, 1999. ⁴⁶ USA III	To determine the efficacy of androgen deprivation given in combination with localised radiotherapy for prostate cancer.		Overall survival. Cancer specific survival.	<p><i>14 Retrospective Studies</i></p> <p>Three of 4 studies that analysed biochemical control rates showed significant improvements in this end-point but conflicting results were obtained for overall survival.</p> <p>No study showed improvement in cancer specific survival.</p> <p><i>6 RCTs</i></p> <p>Only one study showed improvement in overall survival and one in cancer specific survival.</p> <p>No inferential methodologies could be applied to the data owing to substantial differences in study design</p>	<p>Searches were only conducted on one database and only studies published in the English language were included.</p> <p>The review considers an array of study limitations and quality control measures.</p> <p>Although RCTs and retrospective trials were considered separately, there was no other definite quality assessment.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE was searched from January 1980 to September 1998 for English language publications.</p> <p><i>Inclusion criteria</i> Comparisons of radiotherapy alone or in combination with some form of hormonal manipulation.</p> <p><i>Quality assessment</i> Limited information.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes</p>

Table 5.5b: Hormone therapy in cancer of the prostate: RCTs

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Bolla, 1997. ⁵⁰ USA II	A comparison of external irradiation and external irradiation with goserelin in patients with locally advanced prostate cancer.	<p><i>Participants</i> 415 patients under 80 years of age (median age = 71 years) with histologically proven prostatic adenocarcinoma, T1 to T4 with no previous treatment for prostate cancer.</p> <p><i>Intervention</i> Radiotherapy – patients treated once a day five days a week for seven weeks. (50Gy to the whole pelvis with a 20Gy boost to the prostate). Hormonal treatment – Goserelin given subcutaneously every four weeks, starting on the first day of pelvic irradiation and lasting 3 years.</p> <p><i>Design</i> RCT.</p>	<p>Overall survival.</p> <p>Disease-free interval.</p> <p>Time to treatment failure.</p> <p>Toxicity.</p>	<p>Median follow-up 45 months.</p> <p><i>Overall survival at 5 years</i> Combined treatment group – 79% (95% CI: 72% to 86%) Radiotherapy group – 62% (95% CI: 52% to 72%) p = 0.001; HR 0.50 (95% CI: 0.33 to 0.76)</p> <p><i>Disease-free survival at 5 years</i> Combined treatment – 85% (95% CI: 78% to 92%) Radiotherapy group – 48% (95% CI: 38% to 58%) p < 0.001.</p> <p><i>Mortality</i> Radiotherapy 58 deaths (26 owing to prostate cancer) Combined treatment 35 deaths (6 owing to prostate cancer)</p> <p><i>Disease progression (number of patients)</i> Radiotherapy 78, Combined treatment 20</p> <p><i>Five year local control rate</i> Radiotherapy 77% Combined treatment 97% HR 0.19 (95% CI: 0.10 to 0.37, p < 0.001)</p> <p><i>Time to treatment failure</i> Radiotherapy 4.4 years Combined treatment 6.6 years</p> <p><i>Five year failure free rate</i> Radiotherapy 43% Combined treatment 43%</p> <p><i>Toxicity</i> 5% of patients from both groups had grade 3 or 4 toxic effects. Grade 3 or 4 diarrhoea affected 22% (n = 11) in the radiotherapy group.</p>	The study may have been strengthened by the inclusion of a hormone only arm.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Centralised at EORTC data Centre. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Intention to treat analysis used. Survival curves estimated using Kaplan Meier technique. All comparisons made using a two sided log rank test.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Fellows, 1992. ⁵² UK II	To compare the effects of radiotherapy alone, orchidectomy alone and combined therapy on the duration of survival and on the time to appearance of metastases.	<p><i>Participants</i> Patients with localised prostate cancer (T2 to T4, NX, M0).</p> <p><i>Interventions</i> Patients were randomised to radical radiotherapy, orchidectomy or combined therapy.</p> <p><i>Design</i> RCT.</p>	Overall survival. Incidence of metastases. Toxicities.	<p>88 patients were randomised to receive radical radiotherapy, 90 patients were randomised to undergo a radical orchidectomy and 99 patients were randomised to receive combined therapy.</p> <p>32 urologists entered a total of 277 patients from 23 centres.</p> <p><i>Efficacy</i> There was no statistically significant difference in overall survival between the three treatment groups or the need for further treatment for local progression.</p> <p>Incidence of metastases was significantly higher in the radiotherapy alone group (χ^2 13.27, $p < 0.005$) compared with the other two groups.</p> <p>No significant difference in the time to onset of metastases was demonstrated between the groups. Metastases were less frequent with T2 tumours (χ^2 12.27, $p < 0.01$).</p> <p><i>Toxicity</i> 31 patients (16%) had an adverse reaction to orchidectomy; the commonest adverse surgical reaction was hot flushes. 48 patients (26%) had adverse reactions to radiotherapy; 35 patients had bowel symptoms and 15 urinary symptoms.</p>	No description of the extent of orchidectomy or the dose and schedule of radiotherapy was given in the report. The incidence of impotence is not reported.	<p><i>Randomisation</i> Yes. Randomised by telephone.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> The Kaplan-Meier method was used for survival data. Outcome differences were compared with the log rank test and the χ^2 test.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Granfors, 1998. ⁵³ Sweden II	To compare the combination of orchidectomy and radiotherapy to radiotherapy alone in the treatment of prostate cancer.	<p><i>Participants</i> Patients with pelvic confined prostate cancer T1 to 4, pN0 to 3, M0.</p> <p><i>Interventions</i> Patients were randomised to receive definitive radiotherapy (Arm 1 at a dose of 50Gy to the whole pelvis and mean 14.9Gy boost to the prostate) or orchidectomy and radiotherapy (Arm 2 at a dose of 50Gy to the whole pelvis and mean 15.2Gy boost to the prostate).</p> <p><i>Design</i> RCT. Stratified by tumour and nodal status.</p>	<p>Progression-free survival.</p> <p>Disease-specific survival.</p> <p>Overall survival.</p>	<p>91 patients were randomised to the study. Of these, 45 patients were randomised to receive definitive radiotherapy and 46 patients were randomised to undergo a combination of orchidectomy and radiotherapy.</p> <p>Median follow-up was 9.3 years (range 6.0 to 11.4).</p> <p><i>Efficacy</i> Clinical progression was seen in 61% of the radiotherapy only group and 31% in combined therapy group (p = 0.005).</p> <p>Mortality was 61% in radiotherapy alone group and 38% in combined therapy group (p = 0.02).</p> <p>Disease-specific survival was 44% in radiotherapy alone group and 27% in combined therapy group (p = 0.06).</p>	Lymph node negative patients had better prognosis than positive node patients.	<p><i>Randomisation</i> Yes.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Kaplan-Meier plots were used for survival time calculations and were with compared using log-rank test.</p>
Hanks, 2000. ⁵⁶ USA II	To determine the efficacy of long-term androgen suppression following neo-adjuvant hormone cyoreduction and radiotherapy in locally advanced prostate cancer.	<p><i>Participants</i> Patients with locally advanced prostate cancer (T2c to T4) and with PSA levels of less than 150ng/ml .</p> <p><i>Interventions</i> All patients received goserelin and flutamide 2 months before and 2 months during radiation and were then randomised to either 24 months of additional goserelin or no further treatment</p> <p><i>Design</i> RCT.</p>	<p>Disease-free survival.</p> <p>Local progression.</p> <p>Distant metastasis.</p> <p>Biochemical failure.</p> <p>Disease-specific survival.</p> <p>5 year survival.</p> <p>Toxicity.</p>	<p>1,554 patients were evaluated against the inclusion criteria; 34 were found to be ineligible.</p> <p>Median follow-up was 4.8 years.</p> <p>Long-term androgen deprivation group showed a significant improvement in:-</p> <p>Disease-free survival 54% vs 34% (p = 0.001) Local progression 6% vs 13% (p = 0.0001) Distant metastasis 11% vs 17% (p = 0.001) Biochemical failure 21% vs 46% (p = 0.001).</p> <p>54 patients died of prostate cancer on short-term treatment compared with 33 on long-term treatment. The respective disease-specific survival was 87% compared with 92% (p = 0.07).</p> <p>No difference in five year survival.</p> <p>Significant increase in grade 3 and 4 bowel complication with long-term treatment (p = 0.04).</p> <p>In a subset analysis, T3, T4 and T2 with Gleason 8 to 10 showed significant benefit in disease-specific survival with long-term treatment – 90% compared with 86% (p = 0.03).</p>	<p>Large number of patients.</p> <p>In abstract form only.</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Not stated.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
				All patients with Gleason grade 8 to 10 disease had better 5 year survival 80% compared with 69% (p = 0.02) and disease-specific survival – 90% compared with 78% (p = 0.007) with long-term treatment.		
Laverdière, 1996. ⁵⁵ Canada II	To determine the efficacy of combined androgen blockade following EBRT in localised prostate cancer.	Participants Patients with clinical Stage B1 (T2a), B2 (T2b/T2c) and C (T3/T4) adeno-carcinoma of the prostate. Interventions Patients randomised to EBRT alone (group 1) or 3 months of neo-adjuvant combination therapy (LHRH-agonist and flutamide) prior to EBRT (group 2) or combination therapy 3 months before, during and 6 months after EBRT (group 3). Design RCT.	Positive biopsy rate at 12 and 24 months.	120 patients entered. 92 and 62 patients underwent biopsies at 12 and 24 months respectively after the end of EBRT. Residual neoplasm at 12 months Control (group 1) 62%, Group 2 30%, Group 3 4% (p = 0.00005) Residual neoplasm at 24 months Control (group 1) 65%, Group 2 28%, Group 3 5% (p = 0.00001). Serum PSA indicated a significant difference between the 3 groups at 12 months (p = 0.0001), but not at 24 months.	Radiation therapy alone was associated with a higher positive biopsy rate compared with combination. Further clinical trials are needed to define the optimum duration of combination therapy.	Randomisation Yes Stratified by stage, PSA and Gleason score. Allocation concealment Not stated. The report did not state if the study was blinded. Completeness of patient data Yes Appropriate analysis of results Likelihood ratio χ^2 statistics and Kruskal-Wallis test used to compare differences between groups.
Lawton, 2000. ⁴⁹ USA II	To evaluate the potential benefit of androgen ablation following standard external beam radiation therapy in patients with locally advanced prostate cancer.	Participants 977 definitively irradiated patients with histologically confirmed locally advanced carcinoma of the prostate. Interventions Standard external beam radiation therapy followed by androgen ablation. Androgen ablation with goserelin was initiated during the last week of radiotherapy in Arm 1 patients and at the time of relapse in Arm 2 patients.	Local failure, regional failure. Distant metastases and disease-free survival. Biochemical disease-free survival. Absolute survival. Time to distant metastasis or local recurrence.	Median follow-up: 5.6 years for all patients; 6.0 years for living patients At 8 years follow-up:- Local failure Goserelin 23% Radiotherapy 37% p < 0.0001 Distant metastasis Goserelin 27% Radiotherapy 37% p < 0.0001 Disease-free survival Goserelin 36% Radiotherapy 25% p < 0.0001	This study is an update of a phase III RTOG Trial 85-31. No information or data on toxicity was given. The study included patients with pelvic or para-aortic lymph node metastases.	Randomisation Yes Allocation concealment Zelan Method. The report did not state if the study was blinded. Completeness of patient data Yes Appropriate analysis of results Yes. Kaplan Meier method, log rank test and Cox proportional hazard regression model used for statistical

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
		<i>Design</i> RCT.		<p><i>Disease-free survival with PSA < 1.5ng/ml</i></p> <p>Goserelin 32%</p> <p>Radiotherapy 8%</p> <p>p < 0.0001</p> <p><i>Disease-free survival with PSA < 4ng/ml</i></p> <p>Goserelin 35%</p> <p>Radiotherapy 13%</p> <p>p < 0.0001</p> <p><i>Absolute survival</i></p> <p>Goserelin 49%</p> <p>Radiotherapy 47%</p> <p>p = 0.36</p> <p><i>Cause specific</i></p> <p>Goserelin 16%</p> <p>Radiotherapy 21%</p> <p>p = 0.23</p> <p><i>Overall survival</i></p> <p>Goserelin 49%</p> <p>Radiotherapy 47%</p> <p><i>For patients with Gleason score 8 to 10 not undergoing prostatectomy</i></p> <p>A statistically significant improvement in both absolute (p = 0.036) and cause specific (p = 0.019) survival was demonstrated.</p>		used for statistical analysis.

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods												
Pilepich, 2001. ⁵¹ USA II	To determine the efficacy of androgen ablation before and during radiotherapy for locally advanced prostate cancer.	<p><i>Participants</i> Men with bulky prostate carcinoma (T2 to T4) with or without pelvic lymph node involvement and without distant metastases.</p> <p><i>Interventions</i> Patients were randomised to receive either radiotherapy, goserelin (3.6mg every 4 weeks) and flutamide (250mg three times per day. for 2 weeks before and during radiotherapy) (Arm I) or radiotherapy alone (Arm II).</p> <p><i>Design</i> RCT.</p>	<p>Local control.</p> <p>Incidence of metastases.</p> <p>Disease-free survival.</p> <p>Biochemical disease-free survival (PSA < 1.5).</p> <p>Cause-specific survival.</p>	<p>456 evaluable patients were recruited. Of these 226 patients were randomised to Arm I and 230 patients were randomised to Arm II. Median follow-up was 6.7 years.</p> <p><i>Efficacy</i> Androgen ablation improved local control (42% against 30%, p = 0.016), reduced the incidence of distant metastases (34% against 45%, p = 0.04), improved the rate of biochemical disease-free survival (24% against 10%, p < 0.0001) and improved the cause-specific mortality rate (23% against 31%, p = 0.05).</p> <p>A subset analysis indicated that patients with Gleason 2 to 6 disease benefited from a highly significant improvement in all endpoints including survival (70% against 52%, p = 0.015).</p> <p>Patients with Gleason 7 to 10 tumours saw no significant enhancement in local control or survival.</p>		<p><i>Randomisation</i> Yes. Stratified by stage and histological type.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> The Kaplan-Meier method was used for survival data and data were compared using the log-rank test.</p>												
Wirth, 2001. ⁵⁷ Germany II	To evaluate the benefit of Bicalutamide as primary or adjuvant therapy in patients with localised and locally advanced prostate cancer.	<p><i>Participants</i> 3,603 patients with T1b to T4 prostate cancer, of any nodal status. Median follow-up 2.6 years.</p> <p><i>Intervention</i> Bicalutamide as primary or adjuvant therapy compared with radiotherapy or active monitoring.</p> <p><i>Design</i> RCT.</p>	<p>Time to progression.</p> <p>Overall survival.</p>	<p><i>Clinical progression</i></p> <table border="0"> <tr> <td>Standard care</td> <td>16.2%</td> </tr> <tr> <td>Bicalutamide</td> <td>10%</td> </tr> </table> <p><i>Progression-free HR</i> 0.57 in favour of Bicalutamide, p < 0.0001.</p> <p>Any disease progression:-</p> <p><i>Patients with localised disease</i></p> <table border="0"> <tr> <td>Standard care</td> <td>0.2%</td> </tr> <tr> <td>Bicalutamide</td> <td>8.6%</td> </tr> </table> <p><i>Patients with locally advanced disease</i></p> <table border="0"> <tr> <td>Standard care</td> <td>24.3%</td> </tr> <tr> <td>Bicalutamide</td> <td>12.6%</td> </tr> </table> <p>Survival data immature with 7.2% overall mortality and less than 2% dying of prostate cancer.</p>	Standard care	16.2%	Bicalutamide	10%	Standard care	0.2%	Bicalutamide	8.6%	Standard care	24.3%	Bicalutamide	12.6%	<p>The finding that early androgen deprivation therapy increases progression-free survival is in keeping with data from other studies.</p> <p>Overall survival data are needed to permit more definitive recommendations on timing of hormone therapy.</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Double blind placebo controlled trial.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>
Standard care	16.2%																	
Bicalutamide	10%																	
Standard care	0.2%																	
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Standard care	24.3%																	
Bicalutamide	12.6%																	

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Wirth, 2001. ⁵⁸ Europe, South Africa, Australia and North America II	To investigate the efficacy and tolerability of bicalutamide as immediate therapy or as an adjuvant to therapy of curative intent in prostate cancer.	<i>Participants</i> Men with localised or locally advanced prostate cancer and with negative bone scans. <i>Interventions</i> Bicalutamide (150mg/day) or placebo in addition to standard therapy of radical prostatectomy, radiotherapy or active monitoring. <i>Design</i> Combined data from 3 prospective, double-blind, placebo-controlled clinical trials.	Objective disease progression. Toxicity. Overall survival.	8,113 men were enrolled in 3 trials. Of these 3,292 men were entered in a trial in North America, 1,218 patients were entered in a Scandinavian trial and 3,603 patients were enrolled in a trial recruiting patients from Europe, South Africa and Mexico. Median follow-up was 3 years. <i>Efficacy</i> Bicalutamide significantly reduced the risk of progression by 42% compared with placebo (HR 0.58, 95% CI: 0.51 to 0.66, p = 0.0001). 363 of 922 patients (39.4%) progressed on bicalutamide compared with 559 of 922 patients (60.6%) treated with placebo. The overall mortality was 6% with less than 2% dying of prostate cancer. <i>Toxicity</i> The most frequent side-effects were gynecomastia and breast pain.	The survival data may be viewed as immature.	<i>Randomisation</i> Yes. <i>Allocation concealment</i> Not stated. <i>Completeness of patient data</i> Yes <i>Appropriate analysis of results</i> An intention-to-treat approach to the analysis was utilised. The Cox proportional hazard model was used.
Zagars, 1988. ⁵⁴ USA II	To compare radiotherapy alone with radiotherapy and adjuvant oestrogen therapy in prostate cancer.	<i>Participants</i> Patients with Stage C adenocarcinoma of the prostate. <i>Interventions</i> Radiotherapy alone or radiotherapy and immediate oestrogen. Oestrogen was administered as Diethylstilbestrol. Initially patients were treated with 5mg daily but the dose was reduced to 2mg daily). <i>Design</i> RCT.	Disease-free survival. Overall survival.	82 patients were randomised; of these 40 patients were randomised to receive radiotherapy and 38 patients were randomised to radiotherapy and oestrogen. Median follow-up was 14.5 years. Four randomised patients were excluded from the study; one had no evidence of malignancy, one refused radiotherapy and did not attend follow-up, one was lost to follow-up after completing radiotherapy and one patient as he had developed metastatic disease prior to inclusion in the study. <i>Efficacy</i> Disease-free survival was significantly higher in the adjuvant oestrogen group with rates of 71%, 63% and 63% at 5, 10 and 15 years respectively, compared with 49%, 43% and 35% for the radiation alone group (p = 0.008). There was no improvement in survival.	Small study group.	<i>Randomisation</i> Yes. <i>Allocation concealment</i> Not stated. <i>Completeness of patient data</i> Yes <i>Appropriate analysis of results</i> Intention-to-treat and treatment received analysis were undertaken. Actuarial analysis was used for survival data.

Table 5.6a: A comparison of single agent hormone therapy with orchidectomy: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Agency for Health Care Policy and Research, 1999. ⁶⁰ USA I	To compare the effectiveness of maximal androgen blockade (MAB) with monotherapy as primary treatment for advanced prostate cancer.	<p><i>Participants</i> Men with clinically confirmed advanced prostate cancer, who were not previously treated with hormonal therapy.</p> <p><i>Interventions</i> Monotherapy (orchidectomy, LHRH agonists, anti-androgens) Maximal androgen blockade Immediate and deferred androgen suppression.</p> <p><i>Design</i> RCTs.</p>	<p>Overall survival. Cancer-specific survival. Progression-free survival/Time to progression. Time to hormone refractory status. Time to treatment failure. Adverse effects of treatment. Quality of life. Patient preferences or satisfaction.</p>	<p>27 RCTs were located which enrolled a total of 7,987 patients.</p> <p><i>Monotherapy compared with MAB</i> No difference was seen in overall survival at two years (HR 0.970; 95% CI: 0.866 to 1.087). A significant advantage in overall survival for combined androgen blockade was seen at 5 years (HR 0.871; 95% CI: 0.805 to 0.942). When treatment using non-steroidal anti-androgens was compared with cyproterone acetate for combined androgen blockade, no difference was found (HR 1.168; 95% CI: 0.919 to 1.484). When a non-steroidal anti-androgen was part of the MAB schedule and compared with monotherapy, no significant difference was found (HR 0.926; 95% CI: 0.812 to 1.056). In comparison with monotherapy, when the anti-androgen component of the MAB regime was flutamide (HR 0.945; 95% CI: 0.779 to 1.147) or nilutamide (HR 0.878; 95% CI: 0.564 to 1.368), no statistically significant differences were found. No significant difference between the flutamide and bicalutamide regimes were demonstrated (HR 0.87; 95% CI: 0.72 to 1.05).</p> <p><i>Adverse effects</i> Limited data is available. 10% of patients treated by MAB and 4% of patients treated by monotherapy reported adverse effects.</p> <p><i>Quality of Life</i> Little available data were available although evidence suggests monotherapy is more favourable than combined androgen blockade.</p>	<p>A very comprehensive meta-analysis with a systematic and inclusive search strategy and quality assessment criteria. Survival figures at 5 years were based on limited data.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE, Cancerlit, EMBASE and Current Contents were searched from initiation to August 24th 1998. A full search strategy was provided.</p> <p><i>Inclusion criteria</i> RCTs comparing the relative effectiveness of alternative strategies for androgen suppression as treatment for advanced prostate cancer were included. Phase II studies which reported on withdrawals from therapy and studies reporting quality of life were also included. RCTs which only compared different doses of the same agent were excluded.</p> <p><i>Quality assessment</i> Two independent reviewers assessed collected studies with disagreements resolved by consensus. Quality assessments included an assessment of the method of random sequence generation, of the blinding of the randomisation process during patient recruitment and the blinding of the investigator and patient to treatment allocation prior to breaking the randomisation code, the reporting of withdrawals and the handling of withdrawals in the analysis, the use of intent to treat analysis, the reporting of power analysis calculations, the monitoring of treatment compliance and the description of treatment protocols (including concurrent treatments). Trials were classified as higher quality if they</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
						were double blinded and reported outcomes based on an intention to treat analysis. <i>Study details</i> Yes <i>Appropriate synthesis of results</i> Yes. A meta-analytical combination of overall survival data was conducted using a random effects model. A sensitivity analysis and a test for publication bias were performed.
Seidenfeld, 2000. ⁵⁹ USA I	To determine the effectiveness of LHRH agonist compared with orchidectomy or diethylstilbestrol (DES).	<i>Participants</i> Men with locally advanced or metastatic disease. <i>Interventions</i> Diethylstilbestrol (DES) 3mg; orchidectomy; LHRH agonists (Leuprolide, Goserelin, Buserelin), anti-androgens (non-steroidal anti-androgens including Flutamide, Bicalutamide and the steroidal anti-androgen cyproterone). <i>Design</i> RCTs.	Overall survival. Progression-free survival. Time to treatment failure. Adverse effects. Quality of life. Patient preference.	Overall 24 RCTs were located which included data on in excess of 6,600+ patients. Not all trials report all outcomes. <i>DES compared with orchidectomy</i> 3 RCTs addressed this question and these included 1,302 patients. No statistically significant differences in median 2 or 5 year survival rates were seen. <i>LHRH compared with orchidectomy or DES</i> 10 RCTs with a total of 1,908 patients were located. In nine of the ten trials no difference was seen in overall survival. Relative to orchidectomy, no significant differences were found in overall survival hazard ratios for leuprolide (HR 1.1, 95% CI: 0.21 to 5.84), buserelin (HR 1.13, 95% CI: 0.53 to 2.40), goserelin (HR 1.12, 95% CI: 0.90 to 1.39) or combined LHRH (HR 1.26, 95% CI: 0.92 to 1.39). In 4 of 5 trials which reported progression-free survival, no statistically significant differences between groups were found. The control arm was superior to the intervention arm in the remaining trial (p = 0.05). No significant differences between the groups were found in relation to the time to treatment failure. <i>Anti-androgen compared with orchidectomy</i> DES or LHRH:- 13 RCTs which enrolled a total of	Well described, rigorous systematic review and meta-analysis. The meta-analysis has been conducted with appropriate caution and includes sensitivity analyses using disease stage and better quality studies. The results are presented clearly although only graphically in the report. The pooled hazard ratios for 2 year overall survival compared with orchidectomy are taken from the abstract.	<i>Review question</i> Yes <i>Literature search</i> MEDLINE, Cancerlit, EMBASE and Cochrane were searched to March 1998 while Current Contents was searched to August 1998. Strategy provided. <i>Inclusion criteria</i> RCTs which incorporated efficacy related <i>Outcomes</i> were included. Comparisons of monotherapy with an LHRH agonists and monotherapy with orchidectomy or DES; monotherapy with an anti-androgen and monotherapy with orchidectomy, DES or an LHRH agonist were included. Studies were included if they investigated men with advanced prostate cancer including regional or disseminated metastases. <i>Quality assessment</i> Sources of bias; use of blinding; adequacy of concealment of allocation, documentation of withdrawals, intention to treat analysis. <i>Study details</i> Yes

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
				<p>3,840 patients were located. Overall survival was reported in 8 RCTs (2,717 patients). In 1 of 3 studies studying flutamide and 2 of 5 investigating bicalutamide the control arm showed statistically significant increase in survival.</p> <p>No significant differences were seen between the groups in the remaining studies.</p> <p>The 2 year hazard ratio for overall survival relative to orchidectomy was 1.22 (95% CI: 0.99 to 1.50).</p> <p>In relation to progression-free survival and time to treatment failure, of 2 trials comparing bicalutamide with castration, one significantly favoured bicalutamide, the other the control arm. Other trials found no difference between arms or favoured control.</p> <p>Fewer withdrawals among those treated with LHRH agonists (0% to 4%) than non-steroidal anti-androgens (4% to 10%) were recorded. The rate of withdrawal was highest for flutamide (9.8%) among the anti-androgens mainly because of gastrointestinal intolerance.</p> <p>2 of 13 studies addressed quality of life issues using a validated measurement tool (Health Related Quality of Life Scale). Patients in the bicalutamide groups showed greater improvements from pre-treatment measures of sexual interest and physical capacity than controls offered surgical or chemical castration (p < 0.01).</p> <p>In 2 of the 13 studies, 285 patients who were offered the choice of orchidectomy or LHRH agonist; 31% chose orchidectomy.</p> <p>18 studies were included in the meta-analysis.</p>		<p><i>Appropriate synthesis of results</i></p> <p>Yes. Meta-analyses combined data on 2 year overall survival using a random effects model and reported results as a hazard ratio relative to orchidectomy. Tests of heterogeneity and sensitivity analyses were undertaken.</p>

Table 5.6b: A comparison of single agent hormone therapy with orchidectomy: RCTs

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Iversen, 2000. ⁶¹ UK II	To determine the efficacy of non-steroidal monotherapy compared with orchidectomy in non-metastatic locally advanced prostate cancer.	<p><i>Participants</i> 480 patients with PSA levels greater than 20ng/ml and T3/T4 locally advanced (M0) prostate cancer, who had undergone no previous systemic therapy.</p> <p><i>Intervention</i> Bicalutamide monotherapy (150mg) compared with orchidectomy (medical or surgical).</p> <p><i>Design</i> RCT.</p>	<p>Time to death and objective progression (assessed at 4, 8 and 12 weeks after randomisation and afterwards at 12 week intervals).</p> <p>Quality of life (assessed at 4, 12, 24 and 48 week intervals).</p>	<p>A median follow-up of 6.3 years was reported by the study.</p> <p>The overall mortality was 56%. No statistical difference in overall survival was found between the two groups (HR 1.05; 95% CI: 0.81, 1.36 p = 0.70). The estimated median survival rates were, for Bicalutamide, 63.5 months and, for Orchidectomy, 69.9 months</p> <p>Disease progression occurred in the cases of 77% of patients (n = 368). No statistically significant difference in time to progression between the two treatment groups (HR 1.20; 95% CI: 0.96, p = 0.11).</p> <p>A statistically significant quality of life benefit was found in patients entered into the Bicalutamide arm, in relation to sexual interest (p = 0.029) and physical capacity (p = 0.046). Differences in favour of bicalutamide were also found in 6 other categories although they did not achieve statistical significance.</p> <p>The highest incidences of adverse effects included hot flushes among the orchidectomy group and breast pain and gynecomastia among the bicalutamide group breast pain and gynecomastia.</p> <p>A low incidence of withdrawals owing to drug related adverse events was noted in the bicalutamide group, 1.3% (n = 4). No new safety issues were identified; 150mg of Bicalutamide was well tolerated.</p>		<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated. The study was not blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> A pooled analysis of two multicentre RCTs of identical design. Efficacy and quality of life data analysed on an intention to treat basis.</p> <p>Time to death and time to progression were analysed using Cox proportional hazards model and Kaplan Meier plots.</p>

Table 5.7a: Immediate compared with deferred treatment: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Agency for Health Care Policy and Research, 1999. ⁶⁰ USA I	A comparison of immediate and deferred androgen deprivation therapy.	<p><i>Participants</i> Men with clinically confirmed advanced prostate cancer, who were not previously treated with hormonal therapy.</p> <p><i>Intervention</i> Monotherapy (orchidectomy, LHRH agonists, anti-androgens) Combined androgen blockade Immediate and deferred androgen suppression.</p> <p><i>Design</i> RCTs.</p>	<p>Overall survival. Cancer-specific survival. Progression-free survival/Time to progression. Time to hormone refractory status. Time to treatment failure. Adverse Effects of treatment. Quality of life. Patient preferences or satisfaction.</p>	<p>3 trials comprising of 1,209 patients were located which assessed the relative roles of immediate primary hormonal therapy against deferred therapy at 5 years in patients with locally advanced or asymptomatic metastatic disease. No significant difference was found between the schedules (HR 0.914; 95% CI: 0.815 to 1.026). When immediate hormonal therapy used as an adjuvant to radiation therapy was compared with deferred hormonal therapy (4 trials, 1,529 patients), a significant reduction in mortality was associated with immediate hormonal therapy – HR 0.631 (95% CI: 0.479 to 0.83). No quality of life data were available from these trials.</p>	<p>This review was a very comprehensive meta-analysis with a systematic and inclusive search strategy and quality assessment criteria. The review was based on published series. The study may not have captured all available information as a result.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE, Cancerlit, EMBASE and Current Contents were searched from initiation to August 24th 1998. A full search strategy was provided.</p> <p><i>Inclusion criteria</i> RCTs comparing the relative effectiveness of alternative strategies for androgen suppression as treatment for advanced prostate cancer were included. Phase II studies which reported on withdrawals from therapy and studies reporting quality of life were also included. RCTs which only compared different doses of the same agent were excluded.</p> <p><i>Quality assessment</i> Two independent reviewers assessed collected studies with disagreements resolved by consensus. Quality assessments included an assessment of the method of random sequence generation, of the blinding of the randomisation process during patient recruitment and the blinding of the investigator and patient to treatment allocation prior to breaking the randomisation code, the reporting of withdrawals and the handling of withdrawals in the analysis, the use of intent to treat analysis, the reporting of power analysis calculations, the monitoring of treatment compliance and the description of treatment protocols (including concurrent treatments). Trials were classified as higher quality if they were double blinded and reported outcomes based on an intention to treat analysis.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes. A meta-analytical combination of overall survival data was conducted using a random effects model. A sensitivity analysis and a test for publication bias were performed.</p>

Table 5.7b: Immediate compared with deferred treatment: primary studies

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Messing, 1999. ⁶⁴ USA II	To determine the efficacy of immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node pathologically positive prostate cancer.	<p><i>Participants</i> 98 men with prostate cancer, who had undergone radical prostatectomy and pelvic lymphadenectomy found to have nodal metastases, median age: 65.6 years, (range: 45 to 78), median Gleason score 7.</p> <p>Patients randomised within 12 weeks of prostatectomy.</p> <p><i>Interventions</i> Immediate androgen therapy with either goserelin (a synthetic agonist of gonadotrophin releasing hormone) or bilateral orchidectomy or observation until disease progression.</p> <p><i>Design</i> RCT.</p>	<p>Death from prostate cancer.</p> <p>Death from other causes.</p> <p>Recurrence.</p> <p>Adverse effects.</p>	<p><i>Death from prostate cancer</i> Observation Group 31.4% Immediate Therapy Group 6.4% HR 6.2 (95% CI: 1.8 to 21.5) p < 0.01</p> <p><i>Death from other causes</i> Observation Group 3.9% Immediate Therapy Group 7.8%</p> <p><i>Recurrence</i> Observation Group 82.3% Immediate Therapy Group 14.9%</p> <p><i>Alive without recurrence</i> Observation Group 17.64% Immediate Therapy Group 76.6% HR 9.7 (95% CI: 4.5 to 21.0) p < 0.001</p> <p><i>Alive with recurrence</i> Observation Group 47% Immediate Therapy Group 8.5%</p> <p><i>Gastrointestinal (patient numbers)</i> Immediate Therapy Group 12 Observation Group 3 p < 0.01</p> <p><i>Non-specific genitourinary adverse effects</i> Immediate Therapy Group 22 Observation Group 5 p < 0.01</p> <p><i>Incontinence</i> Immediate Therapy Group 19 Observation Group 13 p = 0.22</p> <p><i>Hot flushes</i> Immediate Therapy Group 23 Observation Group 0 p < 0.001</p>	<p>PSA measurements were not provided – the use of the PSA assay was not widespread at the time the study protocol was developed.</p> <p>The recruitment goal of 220 patients was not achieved.</p> <p>Analysis was based on intention to treat.</p> <p>The report is of a relatively few events in a small study.</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Intention to treat analysis used and included all patients originally randomised.</p> <p>Descriptive statistical analysis used for patient characteristics.</p> <p>Log rank test Peto and Peto used to compare survival and time to recurrence.</p> <p>Stratified log rank tests used to control differences attributable to the choice of hormone therapy.</p> <p>Cox proportional hazards model used to assess any differences according to race or ethnic group. Survival estimated using Kaplan Meier</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
				<p><i>Gynecomastia</i></p> <p>Immediate Therapy Group 10 Observation Group 1 p < 0.01</p> <p>All the above reported adverse effects were given a grading of 1 or 2 indicating mild adverse effects.</p>		
MRC Prostate Working Party, 1997. ⁶² UK II	To compare immediate compared with deferred hormone treatment for prostate cancer.	<p><i>Participants</i></p> <p>Men with histologically confirmed adenocarcinoma of the prostate.</p> <p>Those with local disease considered too advanced for curative treatment (T2-T4) or with metastases not causing symptoms and a life expectancy 12 months or more.</p> <p><i>Intervention</i></p> <p>Hormone treatment by orchidectomy or LHRH analogue (and anti-androgen for flare). Alternative hormone therapies were permitted if either of these became inappropriate.</p> <p>Hormone treatment was either begun at the time of diagnosis (immediate arm) or when the disease had progressed sufficiently to warrant intervention (deferred arm). Allocation to the immediate or deferred arms was by randomisation.</p> <p><i>Design</i></p> <p>RCT.</p>	Local progression. Distant progression. Complications. Mortality.	<p>934 men were randomised to receive either immediate (469 patients) or deferred (465 patients) hormone therapy.</p> <p><i>Local progression</i></p> <p>65 men underwent TURP in the immediate arm and 141 in the deferred arm for the management of local progression (p < 0.001).</p> <p><i>Distant progression</i></p> <p>In those with M0 disease, 96 patients in the immediate arm and 144 patients in the deferred arm developed metastases or died from prostate cancer (p < 0.001). In total, 121 patients (26%) in the immediate arm and 211 patients (45%) in the deferred arm developed pain from metastatic disease. (This demonstrated a significant advantage to patients treated immediately, p < 0.001).</p> <p><i>Mortality</i></p> <p>67% of deaths were ascribed to prostate cancer.</p> <p>203 men (43.3%) in the immediate arm and 257 men (55.3%) in the deferred arm died of prostate cancer (p = 0.001).</p> <p>In those with M0 disease, 81 of 256 (31.6%) in the immediate arm and 119 of 244 (48.8%) in the deferred arm died of prostate cancer. (p = 0.0003).</p> <p>In men with metastatic disease at randomisation, there was no significant difference in survival between the two arms.</p> <p><i>Complications</i></p> <p>37 men in the immediate arm and 55 in the deferred arm developed major complications (p < 0.05). Complications were pathological fracture, cord compression, ureteric obstruction and extra-skeletal metastases. In each complication subset not all comparisons were significant.</p>	<p>Participating clinicians continued to treat according to their normal practice with the exception of the hormones.</p> <p>Some of the data on M0 patients may be viewed as immature.</p>	<p><i>Randomisation</i></p> <p>Yes. Telephone registration.</p> <p><i>Allocation concealment</i></p> <p>Not stated.</p> <p><i>Completeness of patient data</i></p> <p>Yes.</p> <p><i>Appropriate analysis of results</i></p> <p>The Kaplan-Meier method was used for time-to-event analysis and data were compared by the log-rank test. Intention-to-treat analysis was used.</p>

Table 5.8a: The role of maximal androgen blockade (MAB) in the management of prostate cancer: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Agency for Health Care Policy and Research, 1999. ⁶⁰ USA I	To compare the effectiveness of maximal androgen blockade (MAB) with monotherapy as primary treatment for advanced prostate cancer.	<p><i>Participants</i> Men with clinically confirmed advanced prostate cancer, who were not previously treated with hormonal therapy.</p> <p><i>Interventions</i> Monotherapy (orchidectomy, LHRH agonists, anti-androgens). Maximal androgen blockade. Immediate and deferred androgen suppression.</p> <p><i>Design</i> RCTs.</p>	<p>Overall survival.</p> <p>Cancer-specific survival.</p> <p>Progression-free survival/Time to progression.</p> <p>Time to hormone refractory status.</p> <p>Time to treatment failure.</p> <p>Adverse effects of treatment.</p> <p>Quality of life</p> <p>Patient preferences or satisfaction.</p>	<p>27 RCTs were located which enrolled a total of 7,987 patients.</p> <p><i>Monotherapy compared with MAB</i> No difference was seen in overall survival at two years (HR 0.970; 95% CI: 0.866 to 1.087). A significant advantage in overall survival for combined androgen blockade was seen at 5 years (HR 0.871; 95% CI: 0.805 to 0.942).</p> <p>When treatment using non-steroidal anti-androgens was compared with cyproterone acetate for combined androgen blockade, no difference was found (HR 1.168; 95% CI: 0.919 to 1.484).</p> <p>When a non-steroidal anti-androgen was part of the MAB schedule and compared with monotherapy, no significant difference was found (HR 0.926; 95% CI: 0.812 to 1.056).</p> <p>In comparison with monotherapy, when the anti-androgen component of the MAB regime was flutamide (HR 0.945; 95% CI: 0.779 to 1.147) or nilutamide (HR 0.878; 95% CI: 0.564 to 1.368), no statistically significant differences were found.</p> <p>No significant difference between the flutamide and bicalutamide regimes were demonstrated (HR 0.87; 95% CI: 0.72 to 1.05).</p> <p><i>Adverse effects</i> Limited data is available. 10% of patients treated by MAB and 4% of patients treated by monotherapy reported adverse effects.</p> <p><i>Quality of life</i> Little available data were available although evidence suggests monotherapy is more favourable than combined androgen blockade.</p>	<p>A very comprehensive meta-analysis with a systematic and inclusive search strategy and quality assessment criteria.</p> <p>Survival figures at 5 years were based on limited data.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE, Cancerlit, EMBASE and Current Contents were searched from initiation to August 24th 1998. A full search strategy was provided.</p> <p><i>Inclusion criteria</i> RCTs comparing the relative effectiveness of alternative strategies for androgen suppression as treatment for advanced prostate cancer were included. Phase II studies which reported on withdrawals from therapy and studies reporting quality of life were also included. RCTs which only compared different doses of the same agent were excluded.</p> <p><i>Quality assessment</i> Two independent reviewers assessed collected studies with disagreements resolved by consensus. Quality assessments included an assessment of the method of random sequence generation, of the blinding of the randomisation process during patient recruitment and the blinding of the investigator and patient to treatment allocation prior to breaking the randomisation code, the reporting of withdrawals and the handling of withdrawals in the analysis, the use of intent to treat analysis, the reporting of power analysis calculations, the monitoring of treatment compliance and the description of treatment protocols (including concurrent treatments). Trials were classified as higher quality if they were double blinded and reported outcomes based on an</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
						<p>intention to treat analysis.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes. A meta-analytical combination of overall survival data was conducted using a random effects model.</p> <p>A sensitivity analysis and a test for publication bias were performed.</p>
Bennett, 1999. ⁷⁴ USA I	A meta analysis to assess the survival benefit of maximal androgen blockade (MAB) therapy with flutamide compared with castration alone.	<p><i>Participants</i> Men with advanced prostate cancer undergoing androgen deprivation therapy. Mean age between 70 and 75 years.</p> <p><i>Interventions</i> Castration (orchidectomy, goserelin, leuprolide). Maximal androgen blockade (MAB) (castration and flutamide 250mg three times per day).</p> <p><i>Design</i> Phase III RCTs.</p>	Overall survival.	<p>9 RCTs were located. The total number of patients in the trials was 4,128.</p> <p>Overall survival: A pooled estimate showed a 10% overall improvement in survival with flutamide (RR 0.90; 95% CI: 0.79 to 1.00)</p>	<p>Lack of methodology and search information makes it difficult to assess the quality of this meta analysis.</p> <p>Limited information on patients' characteristics and search strategy were given.</p> <p>Published studies only were included.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> Update of PCTCG meta-analysis. No other search details. Only peer reviewed studies included.</p> <p><i>Inclusion criteria</i> Yes but not specified.</p> <p><i>Quality assessment</i> No details.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes. Direct estimates of hazard ratios were used. When these were not available, the estimate of log rank statistic and log hazard ratio and the discrete proportional hazard model based on life tables were used. Estimates were combined in random effects meta-analysis (DerSimonian and Laird).</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Bertagna, 1994. ⁷² France I	To determine the efficacy of the combination of anti androgen nilutamide and orchidectomy to treat patients with Stage D prostate cancer who have received no previous treatment.	<p><i>Participants</i> Histologically proven prostate cancer with metastases. None had previously received hormonal treatment.</p> <p><i>Interventions</i> First-line treatment with orchidectomy and nilutamide (300mg/day) or placebo.</p> <p><i>Design</i> Double-blind RCTs.</p>	Response rate. Time to progression. Time and cause of death. Bone pain (5 point scale). Performance status (ECOG scale or Karnofsky index). Symptoms of urinary obstruction. Prostatic acid phosphatase. Alkaline phosphatase.	<p>7 double-blind RCTs were located. 1,056 patients meet the inclusion criteria.</p> <p>A greater proportion of the patients in the nilutamide group than those in the placebo group showed objective response (partial or complete regression: 50% compared with 33% $p < 0.001$).</p> <p><i>Time to progression</i> The percentage of patients whose disease progressed within 6 months after orchidectomy was lower in the nilutamide group (21%) than the placebo group (33%), $p = 0.001$ (OR 0.84; 95% CI: 0.71 to 1.00, $p = 0.05$).</p> <p><i>Death from prostate cancer</i> A 10 % reduction in deaths from prostate cancer was seen in patients receiving nilutamide (OR 0.90; 95% CI: 0.74 to 1.09, $p = 0.292$).</p> <p><i>Bone pain</i> After 6 months more patients given nilutamide than placebo had improved pain control (48% compared with 34%) and fewer had deteriorated (8% compared with 14%, $p < 0.001$).</p> <p><i>Performance status</i> No significant difference between groups was demonstrated.</p> <p><i>Symptoms of urinary obstruction</i> No significant difference was demonstrated between groups.</p> <p><i>Prostatic acid phosphatase (PAP)</i> 81% of nilutamide and 73% of placebo treated groups had improved levels after 6 months ($p = 0.053$).</p> <p><i>Alkaline phosphatase</i> 57% of nilutamide and 42% of placebo treated groups had improved levels after 6 months ($p < 0.001$).</p>	<p>The absence of search details precludes assessment of the comprehensiveness of the meta-analysis. No details of quality assessment are given and there is little information about the review methodology used.</p> <p>The authors state that all the studies were of similar design; one study of divergent design was excluded and did not include one study of different design and duration.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> No strategy provided or details of databases searched.</p> <p><i>Inclusion criteria</i> Long-term randomised studies comparing orchidectomy and nilutamide with orchidectomy and placebo. Only studies investigating patients who had undergone no previous hormonal treatment were included.</p> <p><i>Quality assessment</i> No details</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes. Peto odds ratios and tests for heterogeneity.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Caubet, 1997. ⁷⁵ USA I	A meta analysis of published RCTs to assess the survival benefit of maximal androgen blockade using non-steroidal anti-androgens.	<p><i>Participants</i> Men with prostate cancer (mean age between 70 and 75 years). Men with Stage C and D2 tumours were included.</p> <p><i>Interventions</i> LHRH agonists included goserelin (3.6mg/month); leuprolide (1.0mg/day), buserelin (500µg/day) and the non-steroidal anti-androgens (NSAA): nilutamide (300mg/day) or flutamide (250mg/3 times per day).</p> <p><i>Design</i> RCTs with Chalmers quality scores ranging from 20% to 58%. The median length of follow-up ranged from 6 to 35 months.</p>	Overall survival. Progression-free survival. Tumour response.	<p>13 RCTs (3,427 patients). Estimates of relative risk (RR) when comparing treatment with NSAA and either LHRH or orchidectomy compared with treatment with LHRH or orchidectomy alone.</p> <p>Overall survival could be estimated from 7 trials which compared either LHRH or orchidectomy with the addition of NSAA treatments. Using a proportional hazard model the relative risk was estimated at 0.78 (95%CI: 0.67 to 0.90, $p < 0.001$) while the use of a log hazard ratio estimate gave an estimator of the relative risk of 0.84 (95%CI: 0.76 to 0.93, $p < 0.001$). Both methods found significantly in favour of NSAA.</p> <p>Progression-free survival could be estimated using the proportional hazard model whereby the relative risk was estimated at 0.74 ($p < 0.001$) while the use of a log hazard ratio estimate gave an estimator of the relative risk of 0.77 ($p < 0.001$). Both methods found significantly in favour of NSAA.</p> <p>The pooled tumour response for MAB was 54% and for castration was 45% (OR 0.65, 95%CI: 0.51 to 0.81, $p < 0.0002$).</p>	<p>The review is based only on published studies which may limit its comprehensive-ness.</p> <p>The results have been pooled using two methods, yielding comparable results. In addition quality-based sensitivity analyses were undertaken.</p> <p>It includes a reanalysis of a subset of the PCTCG meta-analysis.⁷⁰</p> <p>Large variation between studies was seen in the percentage of patients with pain, impaired performance status and undifferentiated tumours.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE and Cancerlit were searched to 1996. Current Contents was searched from 1994 to 1995. Bibliographies of relevant articles checked. No language restrictions were applied. Contact with investigators was made where possible. Only published studies included. A strategy was provided.</p> <p><i>Inclusion criteria</i> RCTs comparing treatment with NSAA and either LHRH or orchidectomy against treatment with LHRH or orchidectomy alone.</p> <p><i>Quality assessment</i> The Chalmers scoring system were used although blinding was omitted from the scale.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes. Estimates and standard errors of log hazard ratios for overall survival and progression-free survival were derived. Comparative meta-analyses were performed using the random effects approach of DerSimonian and Laird. Additionally published studies were used in a random effects based meta-analysis of objective tumour response.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
<p>Hucher, 1993.⁷⁶ France I</p>	<p>To perform a meta-analysis of trials comparing orchidectomy and Nilutamide with orchidectomy and placebo in prostate cancer.</p>	<p><i>Participants</i> Patients with Stage D prostate cancer with no previous treatment.</p> <p><i>Intervention</i> All patients underwent an orchidectomy. Patients were randomised to receive nilutamide or to receive a placebo intervention.</p> <p><i>Design</i> Meta-analysis of RCTs.</p>	<p>Disease progression. Bone pain. Marker response. Survival.</p>	<p>Data from 1,056 eligible patients from 7 RCTs were analysed.</p> <p><i>Efficacy</i> In patients receiving nilutamide 50% had a complete or partial regression of disease compared with 33% of patients in the placebo group (p < 0.0001).</p> <p>Bone pain, was significantly improved in patients treated with nilutamide (p < 0.001).</p> <p>Levels of placental alkaline phosphatase and acid phosphatase were improved or returned to normal significantly more frequently in patients treated with nilutamide (p < 0.002 and p < 0.001, respectively).</p> <p>The odds of progression were significantly reduced with nilutamide (OR 0.84, p = 0.05).</p> <p>The odds of death from cancer and from all causes were reduced but not significantly.</p>	<p>Confidence intervals were not reported.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> Published and unpublished RCTs were included. No strategy was reported.</p> <p><i>Quality assessment</i> Not stated.</p> <p><i>Study details</i> Not given.</p> <p><i>Appropriate synthesis of results</i> Treatment groups were compared using the Cochrane-Mantel- Haenszel test stratified by study. Peto's method was used for time to progression and survival.</p>
<p>Iversen, 1997.⁶⁶ Scandinavia I</p>	<p>To critically review the literature on maximal androgen blockade for prostate cancer.</p>	<p><i>Participants</i> Patients with advanced prostate cancer.</p> <p><i>Interventions</i> Maximal androgen blockade (MAB).</p> <p><i>Design</i> Systematic review.</p>	<p>Objective and subjective response. Progression-free survival. Survival.</p>	<p><i>Efficacy</i> A significant advantage with MAB for survival (2 RCTs) and progression-free survival (3 RCTs) was demonstrated.</p> <p>5 studies reported evidence of improved objective or subjective response (PSA/PAP symptoms) with MAB.</p> <p>Where advantages were reported for MAB, the anti-androgen used was a non-steroidal anti-androgen.</p> <p>2 large trials (US and European) indicate MAB prolongs progression-free and overall survival. A further large trial reports significant subjective and objective responses with MAB.</p> <p>A large number of well-conducted trials have not found MAB to be superior to castration alone.</p> <p>Meta-analysis of 25 trials did not demonstrate MAB to be superior to castration in terms of</p>	<p>No search strategy was given.</p> <p>Discussion on controlled trials lacks quantitative data.</p> <p>No 'p' values were reported.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> Not stated.</p> <p><i>Inclusion criteria</i> None stated.</p> <p><i>Quality assessment</i> Not stated.</p> <p><i>Study details</i> Some details were given.</p> <p><i>Appropriate synthesis of results</i> No formal synthesis was conducted.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
				<p>overall survival. Criticisms of the analysis include that it assessed only survival, no prognostic factors were reported and not all available trials were included in analysis.</p> <p>2 trials report improvement in progression-free and overall survival in patients with minimal disease and good performance status receiving MAB. A third trial showed no difference.</p> <p><i>Toxicity</i> MAB was associated with more adverse effects compared with conventional hormone treatment.</p>		
Iversen, 1990. ⁷⁷ Scandinavia I	To evaluate the efficacy of goserelin and flutamide compared with orchidectomy in the treatment of advanced prostatic cancer.	<p><i>Participants</i> Patients with advanced (metastatic or local) prostate cancer.</p> <p><i>Intervention</i> Orchidectomy or treatment with goserelin (3.6mg as a depot preparation) combined with flutamide (250mg three times per day).</p> <p><i>Design</i> Combined analysis of two similar RCTs (EORTC 30853 and DAPROCA 86).</p>	Disease progression. Survival.	<p>327 patients were randomised in the EORTC trial and 264 patients were randomised in the DAPROCA trial, giving a total number of 591 patients. The median follow-up was 1.5 years (for the EORTC trial) and 2.5 years (for the DAPROCA trial).</p> <p><i>Efficacy</i> Time to objective progression was slightly, but significantly, improved with the combination treatment (p = 0.04). Time from objective progression until death was longer in the orchidectomy group (p = 0.046). No difference in overall survival was found between the two groups.</p>	No toxicity data were reported.	<p><i>Randomisation</i> Yes.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes.</p> <p><i>Appropriate analysis of results</i> The Kaplan-Meier method was used for life-table analysis and data were compared using the log-rank test.</p>
Prostate Cancer Trialists Collaborative Group, 2000. ^{70, 71} Netherlands I	To compare the effects on survival of androgen suppression (castration or LHRH agonists) and maximal androgen blockade in the treatment	<p><i>Participants</i> Men with metastatic (88%) or locally advanced (12%) prostate cancer. Half were over 70 years of age. Most took part in trials of flutamide.</p> <p><i>Interventions</i> Androgen suppression, orchidectomy, buserelin, leuprolide, goserelin or</p>	Mortality rate. Survival probability at 5 and 10 years. Non-prostate cancer deaths.	<p>27 RCTs were located and these included 8,275 patients. 12 of these trials involved flutamide and these included 4,803 patients.</p> <p><i>Overall mortality</i> Androgen suppression 72.4% Maximal androgen blockade 70.4% Absolute difference 2% (SE 1.0, p = 0.11)</p> <p><i>5 year survival probability</i> Androgen suppression 23.6%</p>	31 eligible trials were located but data not available for 4 of these (183 patients). Extensive methodology.	<p><i>Review question</i> Yes.</p> <p><i>Literature search</i> Computerised databases, trial registers and meeting abstracts searches were conducted. Researchers and industry professionals were contacted.</p> <p><i>Inclusion criteria</i> Properly RCTs which began before 1991 involving unconfounded comparisons of androgen suppression (surgical or medical) alone compared with castration and additional treatment with anti-</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
	of advanced prostate cancer.	decapeptyl and placebo. Maximal androgen blockade –androgen suppression and nilutamide (150mg/day or 300mg/day), flutamide (750mg/day), cyproterone acetate (CPA) (100mg/day to 300mg/day). <i>Design</i> RCTs where anti-androgen had been administered for 1 year or until progression.		Maximal androgen blockade 25.4% Absolute difference 1.8% (SE: 1.3). No significant improvement in mortality was seen. By 10 years almost all will have died in both groups. <i>Overall mortality by different anti-androgens</i> Nilutamide 0.92 (SE 0.06 2 p = 0.14) Flutamide 0.92 (SE 0.03 2 p = 0.02) CPA 1.13 (SE 0.06 2 p = 0.04) Non-prostate cancer deaths (although not clearly significantly affected by treatment) accounted for some of the apparently adverse effects of CPA.		androgens (flutamide, cyproterone acetate (CPA), nilutamide) Treatment to have lasted at least 1 year. <i>Quality assessment</i> No details. <i>Study details</i> Yes <i>Appropriate synthesis of results</i> Yes. Individual patient data used on intention to treat basis.
Schmitt, 2001. ⁶⁸ USA I	To undertake a systematic review comparing immediate non-steroidal anti-androgens and castration with castration alone for metastatic prostate cancer.	<i>Participants</i> Men with metastatic prostate cancer. <i>Interventions</i> Patients were randomised to be treated with maximal androgen blockade (immediate non-steroidal anti-androgens and castration) or to be treated by castration alone <i>Design</i> Systematic review of RCTs.	Overall survival. Progression-free survival. Cancer-specific survival.	Twenty trials, with a total of 6,320 patients were included in the review. Comparing MAB to castration alone, the pooled odds ratio for overall survival at 1 year was 1.03 (95% CI: 0.85 to 1.25; n = 4,970), at 2 years was 1.16 (95% CI: 1.00 to 1.33; n = 5,286) and at 5 years was 1.29 (95% CI: 1.11 to 1.50; n = 3,550). Progression-free survival was improved at 1 year in patients treated with MAB (OR 1.38, 95% CI: 1.15 to 1.67). Cancer-specific survival was improved at 5 years in patients treated with MAB (OR 1.58, 95% CI: 1.05 to 2.37).	Limited data on quality of life were presented.	<i>Review question</i> Yes. <i>Literature search</i> Data sets from Blue Cross and Blue Shield Association Technology Evaluation Centre, the CCTR, the CENTRAL register and the Cochrane Review Group library were analysed. <i>Quality assessment</i> Yes. <i>Study details</i> Yes. <i>Appropriate synthesis of results</i> Yes. Pooled Odds ratios and Forrest plots were used.

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Schmitt, 1999. ⁶⁷ USA I	To determine the effect of maximal androgen blockade (MAB) on survival when compared with monotherapy (medical or surgical castration alone) for patients with advanced prostate cancer.	<i>Participants</i> Men with advanced prostate cancer, not previously treated with hormone therapy. <i>Interventions</i> Monotherapy: (orchidectomy or LHRH agonist) Maximal androgen blockade (MAB) consisting of flutamide (250mg/3 times per day) or nilutamide (150mg to 300mg/daily) <i>Design</i> RCTs	Overall survival. Progression-free survival. Cancer-specific survival. Adverse events. Quality of life.	20 RCTs were located with a total of 6,320 patients). <i>Efficacy</i> Rates of pooled odds ratios for overall survival were 1.03 (95% CI: 0.85 to 1.25) at 1 year, 1.16 (95% CI: 1.00 to 1.33) at 2 years and 1.29 (95% CI: 1.11 to 1.50) at 5 years. The difference was significant only at 5 years. Progression-free survival was improved only at one year follow-up (OR 1.38; 95% CI: 1.15 to 1.67) and cancer specific survival was improved only at 5 years (OR 1.22; 95% CI: 1.05 to 2.37). <i>Toxicity</i> Adverse effects were more frequent in those assigned to MAB than those assigned to monotherapy and this resulted in the withdrawal of 10% of the patients randomised to MAB. Quality of life was assessed in only one study and favoured orchidectomy alone.	The report details a well structured systematic review.	<i>Review question</i> Yes. <i>Literature search</i> The search strategy involved searching MEDLINE (to 1966), EMBASE (to 1966), Cancerlit (to 1966), the Cochrane Controlled Trials register, the CENTRAL Register, the Cochrane Prostate Disease Register and Current Contents (diskette). <i>Inclusion criteria</i> Published RCTs investigating men with advanced prostate cancer to receive a non-steroidal anti-androgen medication in addition to castration (medical or surgical) or to castration alone and reported overall survival, progression-free survival and cancer-specific survival and/or adverse events. <i>Quality assessment</i> Yes. Concealment of randomisation; completeness of follow-up, outcome assessment; blinded assessment of outcome. <i>Study details</i> Yes. <i>Appropriate synthesis of results</i> Yes.
Dole, 1997. ⁷³ USA III	To determine the efficacy and adverse effects of nilutamide in comparison with current non-steroidal anti-androgen (bicalutamide, flutamide) in advanced	<i>Participants</i> Patients with advanced or metastatic prostate cancer. <i>Interventions</i> Nilutamide or anti-androgens in MAB strategies or as monotherapy. <i>Design</i> Systematic review.	Survival. Disease-free survival. Bone pain. Performance Status. Placental Alkaline Phosphatase (PAP)	<i>Nilutamide and orchidectomy compared with placebo with orchidectomy</i> 4 double blind RCTs were located. 3 of 4 demonstrated significant improvements in bone pain at 6 months. None saw altered PAP at 6 months. In one study, an improvement in performance status at 6 months was seen. 3 of 4 studies saw a significantly increased rate of disease response at 6 months. One study saw a prolonged time to progression. However, no study demonstrated an increase in median	Not many cited studies seem to have used PSA.	<i>Review question</i> Yes. <i>Literature search</i> MEDLINE was searched from 1980 to 1995 and Cancerlit from 1991 to 1995. The terms 'nilutamide', 'flutamide', 'bicalutamide', 'androgen agonists' and 'prostate neoplasms' were used. <i>Inclusion criteria</i> Double blind RCTs with comparable treatment groups with regard to previous therapy and disease

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
	prostate cancer and to estimate the efficacy of non-steroidal anti-androgens in comparison or combination with medical or surgical castration.		concentrations. Adverse effects.	<p>survival time</p> <p><i>LHRH analogues with Non-Steroidal Anti-Androgen</i> 2 RCTs were located. One poorly-reported study compared nilutamide and buserelin or placebo and buserelin. The study reported a significant reduction in bone pain at 1 month owing to nilutamide. The other study (a double blind RCT) found significantly reduced bone pain at day 29 owing to nilutamide and also a decreased time to PAP response.</p> <p><i>Flutamide compared with Placebo and LHRH analogue.</i> Several double blind RCTs were located. One showed a significant increase in progression-free survival and survival owing to flutamide. Five others showed no benefit owing to flutamide over LHRH analogue alone.</p> <p><i>Flutamide and an LHRH analogue compare with orchiectomy alone</i> Two studies were located. One showed significant benefit of MAB in time to first subjective progression, time to progression and median survival time. The other study failed to find a significant difference between the treatments, possibly owing to insufficient power.</p> <p><i>Bicalutamide combined with a LHRH agonist compared with flutamide with a LHRH agonist</i> 1 double blind RCT was located. A significant benefit in favour of bicalutamide was demonstrated in the time to treatment failure, largely owing to high drop-out rate with flutamide (ten-fold excess in diarrhoea over bicalutamide).</p> <p><i>Anti-androgen withdrawal phenomenon</i> 2 studies suggest that about 40% of patients treated with LHRH agonist or orchidectomy and a non-steroidal anti-androgen such as flutamide or</p>		<p>therapy.</p> <p><i>Quality assessment</i> No details given.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
				<p>bicalutamide and who relapse will benefit from withdrawal of the NSAA.</p> <p><i>NSAA as monotherapy</i> Benefit of non-steroidal anti-androgen monotherapy were evaluated in terms of progression, treatment failure, survival and QoL. Compilation of three studies (including an open multicentre RCT) concluded that medical or surgical castration was superior to bicalutamide alone, but there was no significant difference in overall survival. Quality of Life variables favoured bicalutamide over first 3 months and castration over the following 3 months. This may be owing to long-term development of gynecomastia/tenderness caused by bicalutamide.</p> <p><i>Adverse effects</i> Nilutamide:- GI, alcohol intolerance, ophthalmic, pulmonary symptoms were reported. In one trial up to 24% of patients on flutamide experienced diarrhoea.</p> <p>Monotherapy with non-steroidal anti-androgens (but not MAB) usually allows maintenance of libido. Non-steroidal anti-androgens tended to cause gynecomastia and breast tenderness.</p>		

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Laufer, 2000. ⁶⁹ USA III	Critical assessment of maximal androgen blockade compared with surgical or medical castration alone.	<p><i>Participants</i> Patients with confirmed metastatic prostate cancer.</p> <p><i>Interventions</i> Gonadotrophin releasing hormone analogue and anti-androgen compared with gonadotrophin releasing hormone analogue alone. Orchidectomy and anti-androgens compared with orchidectomy. Gonadotrophin releasing hormone analogue and anti-androgen compared with orchidectomy.</p> <p><i>Design</i> Phase III clinical trials.</p>	Survival. Progression free survival. Toxicity. Quality of life. Comparisons of PSA responses.	27 RCTs with a total of 7,987 patients were located. In 24 of the 27 studies there was no significant difference in survival. In the remaining 3 studies, a statistically significant improvement in favour of maximal androgen blockade was reported (p ranged from 0.03 to 0.04).	Little methodological information was presented. No search information or quality assessment criteria were given. No meta-analysis performed.	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> Published results in journals and abstracts – no details were presented.</p> <p><i>Inclusion criteria</i> Phase III clinical trials comparing androgen blockade compared with surgical or medical castration alone</p> <p><i>Quality assessment</i> No details</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes</p>

Table 5.8b: The role of maximal androgen blockade (MAB) in the management of prostate cancer: Primary studies

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Bono, 1998. ⁷⁸ Italy II	To compare the efficacy of chemical castration with maximum androgen blockage (MAB).	<p><i>Participants</i> Men with histologically proven carcinoma of the prostate (Stage C or Stage D).</p> <p><i>Intervention</i> Chemical castration consisted of leuprorelin (a LHRH analogue at a dose of 3.75mg in a depot preparation given subcutaneously every 28 days).</p> <p>MAB consisted of leuprorelin (3.75mg subcutaneously every 28 days) and oral flutamide (an anti-androgen at a dose of 750mg daily).</p> <p><i>Design</i> Multicentre, centrally-controlled, randomised, phase III trial.</p>	<p>Time to treatment failure.</p> <p>Time to disease progression.</p> <p>Overall survival.</p>	<p>214 of 277 recruited patients were evaluable. Median follow-up was 43.7 months.</p> <p>There was no significant difference between chemical castration and MAB in the time to treatment failure, disease progression and overall survival ($p > 0.64$).</p>	<p>There will be a re-analysis of the data when the follow-up time reaches 5 years.</p>	<p><i>Randomisation</i> Yes. Patients were randomised in blocks of 20.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Comparisons between groups (mean and SD) were undertaken with the log-rank, Breslow, Tarone-Ware and χ^2 tests.</p>

Table 5.9a: Second-line treatment for bone pain: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
McQuay, 1997. ⁸⁴ UK I	To evaluate the degree of pain relief achieved following palliative radiotherapy for bone metastasis.	<i>Participants</i> Cancer patients with painful bone metastasis. <i>Interventions</i> External beam radiotherapy or isotopes. <i>Design</i> Published RCTs.	Complete pain relief at 1 month or 50% pain relief at 1 month. 50% pain relief at any time during the study. Speed of onset of pain relief. Comparison of radio-isotopes with external beam radiotherapy.	13 trials were located. 9 reported radiotherapy and 4 reported on isotopes. Radiotherapy induced complete pain relief at 1 month (5 trials) for 368 of 1,373 (27%) patients. This yielded a 'Number Needed to Treat' (NNT) figure of 3.9 (95% CI: 3.5 to 4.4) for external beam radiotherapy. Radiotherapy gave 50% relief at any time in 628 of 1,486 (42%) patients. Median onset in patients' achieving complete relief was 4 weeks. Median duration for complete pain relief was 12 weeks. Radioisotopes alone (192 patients) gave similar results. Fewer new pain sites were reported following Strontium-89.	Textbook review articles and abstracts were excluded and unpublished reports were not sought. Authors were not contacted. NNT based on an assumption about natural history from untreated patients. No meta-analysis was performed.	<i>Review question</i> Yes <i>Literature search</i> MEDLINE was searched from 1966 to 1996. The Oxford Pain Relief data base, EMBASE and the Cochrane library were searched. <i>Inclusion criteria</i> Full articles reporting RCTs were included. A quality scoring system for randomisation, blinding and drop-outs was used. <i>Assessment</i> All authors assessed RCTs independently.
Brundage, 1998. ⁸² USA I/III	To assess the role of Strontium-89 in the management of patients with endocrine refractory carcinoma of the prostate metastatic to bone.	<i>Participants</i> Patients with endocrine refractory carcinoma of the prostate metastatic to bone. <i>Interventions</i> Strontium-89 and Strontium-89 as an adjunct to involved field radiation. <i>Design</i> RCTs.	Markers of successful palliation. Time to further radiotherapy. Patient survival. Treatment toxicity.	4 RCTs. Of these, 2 compared Strontium-89 with placebo, 1 compared Strontium-89 with conventional radiotherapy and 1 evaluated Strontium-89 as an adjuvant to radiotherapy.) One trial showed a significant improvement in pain scores in patients treated with Strontium-89. 2 trials showed significantly fewer new pain sites in the Strontium-89 group compared with external beam radiotherapy. One study showed no significant difference in the proportion of patients with pain relief among patients treated with Strontium-89 as compared with patients treated by the placebo but significantly improved two year survival in patients who had been treated with Strontium-89.	No meta-analysis was performed. Further quality assessment information would have been useful.	<i>Review question</i> Yes <i>Literature search</i> MEDLINE and Cancerlit were searched from 1985 to April 1997. <i>Inclusion criteria</i> Trials including patients with Stage D endocrine refractory cancer, addressing the relevant outcomes. <i>Quality assessment</i> Not stated <i>Study details</i> Yes <i>Appropriate synthesis of results</i> Yes

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Robinson, 1995. ⁸³ USA III	To evaluate the palliative effect and degree of haemotoxicity of Strontium-89 in patients with painful osteoblastic bone metastases.	<p><i>Participants</i> Patients with painful osteoblastic bony metastases primarily from prostate or breast cancer.</p> <p><i>Interventions</i> Palliative treatment with Strontium-89.</p> <p><i>Design</i> Systematic review.</p>	<p>Baseline pain assessment.</p> <p>Platelet and white blood cell counts.</p> <p>Periodic pain estimates.</p> <p>Clinical Response (based on changes in mobility; sleep patterns; ability to work and analgesic intake).</p>	<p>In two uncontrolled studies (n = 393) the majority of patients having bone metastases from breast or prostate (75% to 89%) experienced a reduction in bone pain over 3 months following administration of Strontium-89, while 10% to 18% achieved a complete response (absence of bone pain). The duration of palliation was about 6 months.</p> <p>In an RCT, patients were randomised to receive Strontium-89 or placebo as an adjunct to radiotherapy for bone pain (126 patients with hormone-refractory metastatic prostate cancer). The Strontium-89 arm showed a significant increase in the number of patients reporting no new pain sites (59% as against 34%, p < 0.002), the number that stopped analgesic intake (17% as against 2%, p < 0.05) and the median time to radiotherapy (35 weeks as against 20 weeks, p < 0.006). There was no significant effect on median survival or clinical response owing to Strontium-89.</p> <p>In a UK trial, 305 patients with painful metastatic prostate cancer were randomised to receive Strontium-89, local radiotherapy (n = 148) or hemi-body radiotherapy (n = 157). Pain relief was not significantly different between the arms but in the Strontium-89 arm there was a significant increase in the number of patients reporting no new pain sites (64% as against 42% for local RT, p < 0.005 and 73% as against 51% for hemi-body RT, p < 0.05). The incidence of GI-tract toxicity was significantly higher in the local and hemi-body RT arms.</p> <p>Both the Canadian and UK trials show enhanced haematological toxicity in patients treated with Strontium-89.</p> <p>The interval between re-treatments should be at least 3 months for Strontium-89 and is dependant on the haematological status; some patients have safely been given up to 10 doses of Strontium-89.</p>	<p>A search of only one database was performed. No search strategy provided.</p> <p>Randomised and non randomised studies used.</p> <p>No formal synthesis of results performed.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE was searched from 1966 to 1994.</p> <p><i>Inclusion criteria</i> Studies reporting treatment of patients with painful osteoblastic bony metastases treated with intravenous Strontium-89 as strontium chloride.</p> <p>Evaluation of clinical response, need for pain medication, changes in mobility or sleep patterns were required.</p> <p>Haemotoxicity data were a requirement. A minimum of 10 prostate cancer cases was necessary for study inclusion. Only those studies assessing clinical response following one injection of Strontium-89. At least 3 months follow up was required.</p> <p><i>Quality assessment</i> Not stated.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate Synthesis of Results</i> No formal synthesis was conducted.</p>

Table 5.9b: Second-line treatment for bone pain: RCTs

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Price, 1986. ⁸⁵ UK II	To investigate the efficacy of a single fraction treatment compared with a multi-fraction dose schedule.	<p><i>Participants</i> Patients with histological or cytological evidence of malignant disease with painful bone metastases.</p> <p><i>Interventions</i> Patients were randomised to receive radiotherapy in a single fraction (8Gy) or in a multi-fraction schedule (30Gy in 10 fractions).</p> <p><i>Design</i> RCT.</p>	Onset of pain and duration of response. Mortality. Toxicity.	<p>288 patients were included in the study; of these 140 patients were randomised to receive one 8Gy treatment and 148 patients were randomised to receive 30Gy in 10 treatments.</p> <p>Patients in either group were similar in terms of age, distribution of metastases and diagnosis.</p> <p><i>Efficacy</i> No significant differences in the speed of onset of pain or the duration of response were seen between patients treated with the single fraction treatment and those treated with the multi-fraction therapy.</p> <p>14 patients treated with single fraction radiotherapy were alive at one year. Of these 8 patients (57%) maintained their response. 17 patients who had been treated with multi-fraction radiotherapy survived to one year. Of these, 10 patients (59%) maintained their response. The probability of response was not found to be influenced by the initial severity of pain or the strength of the analgesic required by patients.</p> <p><i>Toxicity</i> No differences were seen in the levels of acute treatment related morbidity between the two arms of the study.</p>	The study included 24 patients diagnosed with prostate cancer and 8 patients with kidney tumours. It also included 71 patients diagnosed with breast cancer, 44 patients diagnosed with lung cancer and 23 patients with myeloma.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Yes</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Tu, 2001. ⁸⁶ USA II	To compare doxorubicin alone (arm D) with doxorubicin in combination with Strontium-89 (arm D/S) in androgen-independent carcinoma of the prostate treated with induction chemotherapy.	<p><i>Participants</i> Patients with progressive androgen-independent prostate cancer affecting bone. Progressive disease defined as worsening of symptoms or increase in PSA.</p> <p><i>Interventions</i> All patients had induction chemotherapy (ketoconazole doxorubicin, estramustine and vinblastine). Patients with stable or responding disease continued doxorubicin and were randomised to receive either Strontium-89 or placebo.</p> <p>Doxorubicin was administered giving 20mg/m² as an infusion over 24 hours once weekly for 6 weeks.</p> <p>Strontium-89 was administered to a dose of 2.035MBq per kg within the first week after doxorubicin.</p> <p><i>Design</i> RCT.</p>	Time to progression (defined as an increase in PSA of 25% above baseline, increase in lesion size or clinical worsening disease).	<p>103 patients were recruited but 31 patients were not randomised. 36 patients were randomised to receive doxorubicin and 36 were randomised to receive both doxorubicin and strontium.</p> <p>Strontium-89 significantly delayed progression (median, 7 months in arm D and 13.9 months in arm D/S, $p < 0.0001$).</p> <p>Strontium-89 significantly increased the overall survival time (median, 16.8 months in arm D and 27.7 months in arm D/S, HR 2.76; 95% CI: 1.44 to 5.29, $p < 0.0014$).</p>	The authors comment that the study is small and cannot provide definitive evidence that the Strontium-89 arm is better than doxorubicin alone.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> No The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes. Intention to treat analysis was used.</p> <p>No subset analysis was undertaken.</p> <p>Time to event analysis was performed using Kaplan-Meier method.</p> <p>Survival curves compared with the log rank test.</p>

Table 5.10a: The role of chemotherapy in the management of prostate cancer: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Casciano, 2001. ⁸⁷ USA III	To undertake a systematic review to evaluate the efficacy of chemotherapy in hormone refractory prostate cancer.	<p><i>Participants</i> Hormone refractory prostate cancer patients.</p> <p><i>Interventions</i> Chemotherapy.</p> <p><i>Design</i> Analysis of published studies.</p>	<p>The primary endpoint was a 50% reduction in PSA levels.</p> <p>Time to progression.</p> <p>Survival.</p> <p>Quality of life.</p>	<p>Overall 52 trials with 2,028 patients were located.</p> <p>19 trials showed a 50% reduction in PSA in more than half of patients (range 53% for estramustine and paclitaxel to 92% for estramustine and docletaxel).</p> <p>In 7 trials of docletaxel in combination with estramustine, PSA levels were reduced in 69.5% of patients. In 3 trials of docletaxel alone, PSA levels were reduced in 47.1% of patients. In 3 trials of vinorelbine in combination with estramustine, PSA levels were reduced in 54.6% of patients. In 4 trials of paclitaxel in combination with estramustine, PSA levels were reduced in 46.4% of patients. In 5 trials of paclitaxel in combination with estramustine and suramin, PSA levels were reduced in 34.9% of patients. In 2 trials mitoxantrone in combination with prednisolone, PSA levels were reduced in 27.6% of patients.</p> <p>Time to progression data was presented in 29 studies. The mean time ranged from 1.9 to 13 months for patients treated with estramustine in combination with docletaxel and dexamethasone.</p> <p>Overall survival data was presented in 21 studies. The mean overall survival data ranged from 7.8 to 27 months for docletaxel monotherapy.</p> <p>4 trials gave a positive pain score suggesting improved quality of life.</p>	<p>The report does not state whether included studies were RCTs.</p> <p>Studies were heterogeneous.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE, Adis, Healthstar, ASCO abstracts, Cancerlit were searched.</p> <p><i>Inclusion criteria</i> Included studies must have information listed outcomes.</p> <p><i>Quality assessment</i> None included</p> <p><i>Study details</i> Not given</p> <p><i>Appropriate synthesis of results</i> No formal statistical analysis.</p>

Table 5.10b: The role of chemotherapy in the management of prostate cancer: RCTs

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
de Reijke, 1999. ⁹⁰ Netherlands II	To compare orchidectomy alone compared with orchidectomy and mitomycin	<p><i>Participants</i> 189 patients with metastatic prostate cancer. Poor prognostic factors. Patients due to begin first hormone treatment by orchidectomy. WHO (World Health Organisation) performance status 1 or 2. Alkaline phosphatase above upper limit normal Or T4 cancer on DRE.</p> <p><i>Intervention</i> Orchidectomy alone. Orchidectomy and mitomycin 15mg/m² iv starting 1 week after orchidectomy.</p> <p><i>Design</i> RCT.</p>	Survival. Time to progression.	<p>189 patients were entered in the study. 93 patients were randomised to orchidectomy alone, 96 patients were randomised to the combined arm. 5 patients were excluded from the analysis</p> <p><i>Efficacy</i> At median follow-up of 4.2 years, 78.8% of patients had died. With respect to time to progression, no difference between the arms for first, subjective or objective progression (p = 0.17, 0.25, 0.08 respectively). The median time to progression was around 1 year in both arms. No differences in progression-free survival was demonstrated (p = 0.67). The median time to progression or death was 1 year. With regard to overall survival, a non-significant trend in favour of orchidectomy alone was seen (median 2 years compared with 1.7 years, p = 0.04, HR 1.43; 95% CI: 1.02 to 1.99).</p> <p><i>Toxicity</i> Substantial thrombocytopenia, leucopenia, pulmonary and gastrointestinal were demonstrated. Seven treatment-related deaths were reported in the chemotherapy arm.</p> <p>Significantly worse quality of life outcomes were seen in the combination arm compared with the orchidectomy only arm.</p>	The study reported a well conducted RCT.	<p><i>Randomisation</i> Not specified.</p> <p><i>Allocation concealment</i> Not applicable.</p> <p><i>Completeness of patient data</i> Yes.</p> <p><i>Appropriate analysis of results</i> Yes</p>
Kantoff, 1999. ⁸⁹ USA II	To compare hydrocortisone alone (arm H) or in combination with mitoxantrone (arm M/H) in hormone-refractory prostate cancer.	<p><i>Participants</i> Men with hormone-refractory metastatic prostate cancer.</p> <p><i>Interventions</i> Oral hydrocortisone at 40mg daily. Intravenous mitoxantrone at 14mg/m² every three weeks.</p> <p><i>Design</i> RCT.</p>	Overall survival. Disease progression or treatment failure. Best clinical response. Reduction in serum PSA. Quality of life.	<p>242 men were recruited. 123 were allocated to receive hydrocortisone only while 119 were allocated to receive both hydrocortisone and mitoxantrone.</p> <p><i>Survival</i> There was no difference in overall survival between the H and M/H arms (12.6 months and 12.3 months respectively, p = 0.77).</p> <p><i>Time to disease progression</i> There was a small but significant advantage to M/H compared with H (the median time to progression was 3.7 months and 2.3 months, respectively, p = 0.022). There was no significant difference in the proportion of patients who ultimately progressed.</p>	The addition of mitoxantrone generated more frequent responses than hydrocortisone alone and a possible benefit in pain control. There was no difference in overall survival.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> No.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
				<p><i>Best response</i></p> <p>There was no significant difference between the two arms in the complete or partial response rates. However, stable disease was more common in patients in the M/H arm than in the H arm (56% compared with 42%, $p = 0.012$).</p> <p><i>Response by PSA</i></p> <p>38% of patients in the M/H arm compared with 22% of patients in the H arm achieved a maximum decrease in PSA of at least 50% ($p = 0.008$, post hoc).</p> <p><i>Quality of life</i></p> <p>There was an indication that the quality of life data were better in the M/H arm. This was especially with respect to pain control though was not true for all other aspects of quality of life.</p>		
Tannock, 1996. ⁸⁸ Canada II	To compare prednisone alone (arm P) with prednisone in combination with mitoxantrone (arm P/M) in symptomatic hormone-resistant prostate cancer.	<p><i>Participants</i></p> <p>Men with hormone-resistant metastatic adenocarcinoma of the prostate with symptoms including pain.</p> <p><i>Interventions</i></p> <p>Prednisone alone (10mg daily).</p> <p>Prednisone and mitoxantrone at 12mg/m² every three weeks. This dose was adjusted by 0 2mg/m² depending on haematological toxicity.</p> <p><i>Design</i></p> <p>RCT.</p>	<p>Palliative response, pain relief and quality of life scores.</p> <p>Disease progression (increase in pain score or clinical progression).</p>	<p>161 patients were recruited from 11 institutions.</p> <p>There was a significant advantage to arm P/M compared with the arm P in the initial palliative response rate (29% compared with 12%, $p = 0.01$) and in the duration of primary response (median 43 compared with 18 weeks, $p < 0.0001$).</p> <p>There was no significant difference in overall survival ($p = 0.27$).</p> <p>52 patients on P alone crossed over to P/M of which 11 (22%) responded for a median duration of 18 weeks.</p>	The authors conclude that chemotherapy with mitoxantrone and prednisone provides palliation for some patients with hormone-resistant prostate cancer.	<p><i>Randomisation</i></p> <p>Yes</p> <p><i>Allocation concealment</i></p> <p>No.</p> <p><i>Completeness of patient data</i></p> <p>Yes</p> <p><i>Appropriate analysis of results</i></p> <p>Yes</p>

Table 5.11: Bisphosphonates in the management of men with bone metastases from prostate cancer – RCTs.

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Dahut, 2001. ⁹⁸ USA II	To determine the efficacy of ketaconazole and hydrocortisone and alendronate compared with ketaconazole and hydrocortisone in patients with androgen independent prostate cancer.	<i>Participants</i> Men with androgen independent prostate cancer. Prior Strontium-89 not permissible. <i>Interventions</i> Patients were randomised to receive either ketaconazole (400mg/three times per day), hydrocortisone 20mg every morning and 10mg every evening) and alendronate (40mg day) or to receive ketaconazole (400mg/three times per day) and hydrocortisone (20mg every morning and 10mg every evening). <i>Design</i> RCT.	Toxicity. PSA response.	Several patients had resolution of bone scan abnormalities. <i>Efficacy</i> 13 of 24 (54%) evaluable patients on ketaconazole and hydrocortisone and alendronate had a 50% decline in PSA compared with 9 of 25 patients (36%) on ketaconazole and hydrocortisone. <i>Toxicity</i> Toxicity in both arms was mild (dry skin, dry eyes, fatigue, mild LFT abnormalities, headaches, nausea and emesis). Several patients in both arms developed 'sticky skin' syndrome.	Ketaconazole, hydrocortisone and alendronate were well tolerated. Accrual continues to further characterise clinical activity.	<i>Randomisation</i> Yes. <i>Allocation concealment</i> Not stated. <i>Completeness of patient data</i> Yes <i>Appropriate analysis of results</i> Yes
Dearnaley, 2001. ⁹⁶ UK II	To determine the efficacy of oral clodronate in delaying symptomatic bone progression and death from prostate cancer.	<i>Participants</i> Patients with prostate cancer commencing or responding to standard hormone treatment. <i>Interventions</i> Patients randomised to either Arm A or Arm B. Arm A consisted of 2,080mg oral sodium clodronate per day. Arm B consisted of a placebo. <i>Design</i> Phase III double-blind, placebo-controlled, randomised trial.	Development of symptomatic bone progression. Death from prostate cancer.	311 patients were randomised over 4 years. 156 patients were randomised to Arm A and 155 to Arm B. Median follow-up was 3 years. Median time on medication was 18 months for patients being treated in Arm A and 16 months for patients being treated in Arm B. Treatment was stopped because of symptomatic bone progression in the cases of 65 patients who had been randomised to Arm A and in the cases of 90 patients who had been randomised to Arm B. 202 patients developed symptomatic bone progression; 93 patients randomised to Arm A and 108 patients randomised to Arm B (HR 0.75, 95% CI: 0.57 to 0.99, p = 0.044). The median time to the development of symptomatic bone disease was 26 months for patients randomised to Arm A and 20 months	Results are preliminary.	<i>Randomisation</i> Yes. <i>Allocation concealment</i> Not stated. <i>Completeness of patient data</i> Yes <i>Appropriate analysis of results</i> Hazard ratio determined for survival data.

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
				<p>for patients randomised to Arm B.</p> <p>83 patients treated in Arm A and 94 patients treated in Arm B have died (HR 0.8, 95% CI: 0.59 to 1.07, p = 0.13). At 2 years median survival is 66% patients treated with sodium clodronate and 59% for patients treated with placebo. Median survival is 34 months in patients treated in Arm A and 27 months for patients treated in Arm B.</p> <p><i>Toxicity</i> Treatment was discontinued owing to adverse effects in the cases of 48 patients randomised to Arm A and in the cases of 27 patients randomised to Arm B.</p> <p>Adverse events were more frequent in patients randomised to Arm A (relative risk 1.79, p =0.0014) and occasioned dose modification in more patients (52 patients from Arm A as against 20 patients from Arm B). Gastrointestinal effects and raised Lactate dehydrogenase (LDH) were the commonest adverse events.</p>		
<p>Saad, 2001.⁹⁷ Canada, Australia, USA II</p>	<p>To determine the efficacy of the bisphosphonate Zometa (Zoledronic acid) in the treatment of bone metastases from prostate cancer.</p>	<p><i>Participants</i> Men with metastatic bone disease from prostate cancer with rising PSA levels despite hormone treatment.</p> <p><i>Interventions</i> Zoledronic acid meta 4mg or placebo every 3 weeks for 15 months.</p> <p><i>Design</i> Randomised phase II double-blind placebo controlled trial.</p>	<p>Skeletal related events (SREs).</p> <p>These are defined as pathological fractures, spinal cord compression, radiation therapy to bone, surgery to bone, need to change chemotherapy to treat bone pain.</p>	<p>422 men were randomised to zometa (214) or placebo (208).</p> <p><i>Median time to first SRE</i> The median time to first SRE was 321 days for placebo patients. The median was not recorded with zometa, p = 0.011. 33% of patients in the zoledronic acid group and 44% of the patients in the placebo group experienced a SRE (p = 0.021).</p> <p>The Mean Skeletal Morbidity rate (SREs/time) was 0.80 for zometa, 1.49 placebo, p = 0.006.</p> <p>15.2 % of patients experienced a elevated serum creatinine compared with 11.5% for the placebo group.</p>	<p>Zoledronic acid appears effective in delaying and reducing complications of bone lesion.</p> <p>The study was published in abstract form only.</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> No methods given.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Smith, 2001. ⁹⁹ USA II	To determine the efficacy of pamidronate in preventing osteoporosis in men with prostate cancer receiving treatment with a gonadotrophin releasing hormone agonist.	<p><i>Participants</i> Men with advanced or recurrent prostate cancer and no bone metastases.</p> <p><i>Interventions</i> Patients were randomised to receive either leuprolide or leuprolide and pamidronate (60mg every 12 weeks).</p> <p><i>Design</i> Open-label randomised trial.</p>	Bone mineral density of lumbar spine and proximal femur (measured by quantitative CT).	<p>47 patients were randomised. 41 completed the study.</p> <p><i>Patients treated with Leuprolide alone</i> With respect to the bone density at baseline, the mean bone density decreased by 3.3% (sd 0.7%) in lumbar spine, 2.1% (sd 0.6%) in the trochanter and 1.8% (sd 0.4%) in the total hip. The mean trabecular bone density of the lumbar spine decreased by 8.5% (sd 1.8%). Each of these comparisons was statistically significant ($p < 0.001$).</p> <p><i>Patients treated with Leuprolide alone and pamidronate</i> No significant change was seen in the mean bone density at any skeletal site.</p> <p><i>Comparisons across the trial arms</i> There were significant differences between the groups in bone density at 48 weeks for lumbar spine ($p < 0.001$), trochanter ($p = 0.03$), total hip ($p = 0.005$) and trabecular bone of the lumbar spine ($p = 0.05$). These favoured the combined treatment.</p>	Only a small number of patients were included in this study.	<p><i>Randomisation</i> Yes.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>

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Testicular Cancer

The Questions

- a) Is there an alternative surgical approach to inguinal orchidectomy in the management of patients with testicular cancers?
- b) What is the optimum curative treatment for Stage I seminoma?
- c) What is the optimum curative treatment for Stage I NSGCT?
- d) What is the optimum curative chemotherapy for metastatic disease?
- e) How effective are radiotherapy and surgery in metastatic disease?

The Nature of the Research Evidence

a) Surgical approach

One review was identified which analysed recurrence rates in patients who underwent scrotal violation as part of their primary surgery for testicular cancer¹ (Table 6.1). No additional RCTs or other relevant publications were identified.

b) Stage 1 seminoma

No meta-analyses have been identified which address the management of Stage I seminoma. However, four RCTs of various aspects of adjuvant radiotherapy were found²⁻⁵ (Table 6.2). Two of these were studies of anti-emetics;^{2,3} the third was a trial comparing two radiotherapy field sizes⁴ and the fourth trial compared two radiotherapy dose levels.⁵

Three studies which have examined the incidence of second malignancies following adjuvant radiotherapy have been reviewed.⁶⁻⁸ A number of observational studies of surveillance in Stage I seminoma were identified.⁹⁻¹¹ A retrospective analysis which captures the data on relapse rates from three major institutions relating to the prognostic factors for relapse on surveillance was identified.¹²

No data from RCTs on the use of adjuvant carboplatin in the management of Stage I seminoma are available, though two relevant observational studies were identified.¹³⁻¹⁵ No RCTs of the three options (radiotherapy, carboplatin or surveillance) has yet been published, but the Medical Research Council's RCT TE19 comparing radiotherapy with a single cycle of carboplatin has closed to recruitment and is likely to report in two years' time. Quality of life data will be reported in the forthcoming MRC TE18 and TE19 RCTs. One quality of life study after radiotherapy or surveillance has been identified.¹⁶

c) Stage 1 NSGCT

One RCT was identified comparing surveillance with adjuvant radiotherapy for Stage I NSGCT¹⁷ (Table 6.3). Three observational studies of surveillance or adjuvant chemotherapy were identified¹⁸⁻²⁰ (Table 6.4). One RCT of adjuvant chemotherapy for pathologically staged patients with microscopic lymph node metastases is included, as it generated the hypothesis leading to studies of adjuvant chemotherapy in clinical Stage I disease²¹ (Table 6.5). This study addressed adjuvant chemotherapy for patients with pathologically proven lymph node metastases from NSGCT.²² This was also addressed by another RCT²³ (Table 6.5).

One study has examined treatment preferences, as an adjunct to a study of adjuvant chemotherapy.²⁴ Retrospective analyses have been used to identify which patients have a higher than average risk of relapse on surveillance.²⁵

An alternative management strategy for Stage I NSGCT in the USA has been retroperitoneal lymph node dissection (RPLND). No RCTs comparing RPLND with surveillance or with adjuvant chemotherapy alone have been identified. This policy has never been adopted in the UK and has not been further included in this review.

d) Chemotherapy for metastatic disease

A number of randomised and non-randomised studies have examined chemotherapy regimes in metastatic testicular germ cell tumours. This review has not considered regimes in use prior to the introduction of the triple drug PVB regime in 1976.

The studies encompass debulking surgery prior to chemotherapy,²⁶ maintenance chemotherapy after remission induction,^{27, 28} adjuvant chemotherapy for patients with pathologically proven lymph node metastases from NSGCT,²² standard chemotherapy for good prognosis disease,²⁹ omission of bleomycin,³⁰⁻³⁶ the substitution of carboplatin for cisplatin³⁷⁻³⁹ or a reduction in the number of treatment cycles.^{40, 41} For patients with intermediate or poor prognosis disease, studies include high dose chemotherapy,⁴²⁻⁴⁵ dose intensification⁴⁵⁻⁴⁸ or the addition of extra agents.^{49, 50} Details of these studies are presented in Table 6.5 (for patients with good prognoses) and Table 6.6 (for studies investigating patients with poor prognoses).

Preliminary results of an RCT comparing BEP with the combination of cisplatin, doxorubicin, cyclophosphamide, vinblastine and bleomycin (CI:SCA/VB) were located.⁵¹

One study was identified which examines the role of high as against low dose vinblastine, in combination with bleomycin and cisplatin in patients with disseminated NSGCT who have good prognosis⁵² (Table 6.5).

The international, pooled analysis of prognostic factors in metastatic germ cell tumours has been included as it forms the basis for the clinical classification of these tumours in current clinical use in the UK.⁵³ One unpublished systematic review of RCTs including or omitting bleomycin was identified⁵⁴ (Table 6.7).

For patients with metastatic seminoma, single agent carboplatin has been compared with combination chemotherapy.^{55, 56} The role of cisplatin in this group of patients has also been investigated^{44, 45, 57} (Table 6.8).

The morbidity of treatment for testicular cancer has been studied in one meta-analysis⁵⁸ (Table 6.9). Additionally several observational studies were identified.⁶⁻⁸ A formal systematic review of all observational studies of the adverse effects of treatment was not done as part of this review and the observational studies should be considered of illustrative use only.

e) Radiotherapy and surgery for metastatic disease

Radiotherapy has been extensively used in the curative treatment of Stage II seminoma (metastases in infradiaphragmatic lymph nodes), but no RCTs in this uncommon stage of disease have been identified. The literature on radiotherapy for Stage II seminoma have been reviewed in one recent publication⁵⁹ and one pilot study of combined neo-adjuvant carboplatin and radiotherapy has been identified.⁶⁰

The role of radiotherapy for residual masses following chemotherapy for metastatic seminoma has been retrospectively studied using pooled data submitted by ten European centres, representing all available data on patients treated between 1978 and 1990 in those centres (Table 6.10).⁶¹ The role of radiotherapy in the management of metastatic disease at other sites has not been extensively studied. One RCT compared surveillance with adjuvant radiotherapy in patients with Stage I NSGCT.¹⁷ A retrospective multivariate analysis of radiotherapy for brain metastases was identified, based on pooled data from European centres.⁶² One RCT evaluating radiotherapy in metastatic disease has been identified, in which patients with Stage II disease were randomised to chemotherapy alone or 'sandwich' chemotherapy and radiotherapy⁶³ and a second RCT compared maintenance chemotherapy with adjuvant radiotherapy after induction chemotherapy for metastatic NSGCT.⁶⁴

The role of surgery for residual NSGCT masses following chemotherapy has been established in observational studies.⁶⁵⁻⁶⁷ No RCTs have been identified.

Summary of the Research Evidence

a) Surgical approach

A systematic review of scrotal violation examined seven studies with data on 1,182 patients. Although it appears to have reported on all published series between 1958 and 1993, no search strategy or further information about the selection of articles was provided.¹ Scrotal violation did not appear to increase the risk of distant relapse in patients with Stage I disease (9.8% compared with 12%, $p = 0.24$) or to affect survival (91.5% compared with 92.7%, $p = 0.33$). There was, however, an increased risk of local relapse in patients who suffered scrotal violation; the absolute risk was not high (2.9% compared with 0.4%, $p < 0.001$).

Conclusion

Though the risks of scrotal violation may be small, there is no evidence to discontinue inguinal orchidectomy as the standard surgical approach.

b) Stage 1 seminoma

Cure rates for patients with Stage I seminoma are reported to be between 96% to 100%, irrespective of whether patients are managed by adjuvant radiotherapy or by surveillance.^{4, 9-11} Non-randomised, retrospective analysis has suggested that it may be possible to identify patients at higher risk of relapse on surveillance.¹² Data were collected from 549 individual patients managed by surveillance in three centres. The five year relapse-free rate were 83%. The tumour size and rete testis invasion status were significant prognostic factors for relapse.¹²

The efficacy of adjuvant radiotherapy is illustrated by the MRC trials.^{4, 5} The short-term effects of adjuvant radiotherapy include nausea and vomiting,³ while in the longer term there is evidence that patients are at increased risk of second malignancies, cardiovascular and renal disease.⁶⁻⁸ In addition, adjuvant radiotherapy and surveillance have some, albeit relatively mild, impact on quality of life.¹⁶ There is evidence, however, that reducing the radiotherapy field to a para-aortic field (irradiation of the para-aortic nodes) from a 'dogleg' field (irradiation of the same area with an extension of the field to include common iliac nodes) does not compromise outcomes and is less toxic.⁴ In this study, 478 men were randomised to adjuvant radiotherapy with one of the fields previously stated. Three year survival rates were 99.3% for the para-aortic field arm and 100% for the dogleg field arm. The relapse-free survival was 96% and 96.6% respectively.⁴ Further reductions in radiotherapy treatment intensity also appear to be possible, as the preliminary results of an MRC RCT comparing a dose of 30Gy with a dose of 20Gy has been presented.⁵ In this trial of 600 patients, the preliminary results suggest that a substantial difference in relapse rates is unlikely.

The acute toxicity of adjuvant radiotherapy includes nausea and vomiting and there is good quality evidence that this can be reduced by prescribing 5-HT₃ antagonist anti-emetics.^{2, 3} More prospective information on the toxicity of adjuvant radiotherapy will be available when the MRC TE18 and TE19 trials publish their results in full. The excess risks of second malignancies in Stage I seminoma patients treated with adjuvant radiotherapy is now well described, probably translating into a two to three fold excess relative risk.^{7, 8}

The use of one or two cycles of adjuvant carboplatin as an alternative to radiotherapy has been piloted¹³⁻¹⁵ and has now been compared with adjuvant radiotherapy in 1,600 patients in an MRC RCT. The first analysis of this trial is due in two to three years' time.

Conclusion

Survival for patients with Stage I seminoma following orchidectomy is likely to be similarly high whether they are managed by surveillance or adjuvant radiotherapy and the advantages and disadvantages of each approach need to be weighed. Adjuvant carboplatin is conceptually unlikely to be associated with inferior survival, but the outcome of current studies is awaited.

c) Stage 1 NSGCT

Cure rates for patients with Stage I NSGCT managed by surveillance are reported to be between 95% and 100%, owing to the effective salvage of the 25% of patients who relapse.¹⁸ The addition of abdominal radiotherapy to surveillance

was tested in an RCT of 150 patients and shown not to improve on these survival rates.¹⁷ However, patients with Stage I disease are not a homogeneous group; a retrospective multivariate analysis of the MRC database has suggested that patients with lympho-vascular invasion in their primary histology are at higher risk of relapse²⁵ with 45% of such patients relapsing within two years. However, because of the effectiveness of salvage treatment, this has no influence on the overall cure rates.

In the United States, where retroperitoneal lymph node dissection has been employed more than in the United Kingdom, two RCTs have evaluated the role of two cycles of chemotherapy in patients with pathological Stage II disease (i.e. positive para-aortic nodes). One study randomised patients to two cycles of PVB or VAB-6 compared with surveillance and showed significantly reduced recurrence rates in the chemotherapy arm although there was no overall survival difference.²¹ A second trial compared two cycles and four cycles of PVB in pathological patients with Stage II disease and showed no significant difference in overall survival.²³ The relevance of these studies is that they suggested that, for patients with microscopic metastatic disease, two cycles of chemotherapy might be enough to effect a cure, in contrast to the (then) standard of four cycles for macroscopic metastatic disease. Therefore, in theory, those patients with clinical Stage I disease but with occult, microscopic metastases (around 25% overall of patients with Stage I disease) could be treated with two cycles of chemotherapy adjuvantly, as an alternative to waiting until disease presented clinically and treating with four cycles.

This rationale was transferred in the MRC studies of two cycles of adjuvant BEP or BOP in patients with Stage I NSGCT germ cell tumours, deemed to be at high risk of recurrence, which reported substantially reduced recurrence rates (from 45% to around 2%) compared with historical controls, albeit not in RCTs.^{19, 20} It is unlikely that this impacts on the overall survival rates, however.

Despite research having been conducted on the factors which influence decision-making in patients and professionals, no statements can be made regarding the quality of life implications of such a policy.²⁴

Conclusion

Surveillance remains a satisfactory option for patients with Stage I NSGCT and adjuvant chemotherapy for patients at high risk of relapse is an alternative option.

d) Chemotherapy for metastatic disease

Patients with metastatic germ cell tumours are generally stratified into prognostic subgroups, based on retrospective analyses such as that of the International Germ Cell Cancer Collaborative Group.⁵³ This is the largest retrospective study, based on an international collaboration which assembled a database of over 6,000 patients treated with chemotherapy in the cisplatin era, resulting in the definition of a good (90% cure), intermediate (80% cure) and poor (45% cure) prognostic group.

RCTs are generally now restricted to one or more specified prognostic groups. Some trials classified patients according to one of the then prevailing prognostic

classification systems and there may, therefore, be differences in the case mix between studies.

The drug combination of cisplatin, bleomycin and vinblastine (PVB) was rapidly established in the 1970's as an effective, curative regime for metastatic germ cell tumours. Bleomycin, etoposide and cisplatin (BEP) were introduced as an alternative to PVB and was reported to be superior in terms of survival and toxicity in an RCT.²² Since then, it has become the most commonly used regime, leading to its use as a control arm in RCTs.^{48, 50} For this reason, some RCTs comparing older regimes or variations of an older regime such as PVB, are not further considered as the use of BEP has rendered them obsolete.⁵² Another alternative to BEP is cisplatin, vincristine, methotrexate, bleomycin, adriamycin, cyclophosphamide and etoposide (POMB-ACE),⁶⁸ particularly for poor risk patients, but no RCTs have been found specifically comparing this with BEP. However, the long-term results of POMB-ACE appear to be broadly similar to those after more intensive regimes such as high dose chemotherapy.⁶⁸

The long-term results of BEP chemotherapy for good-prognosis patients at the Royal Marsden Hospital have been described.⁶⁵ This study reported on 121 men treated between 1979 and 1986. Long-term follow-up (median 65 months) showed an overall five year survival of 87.2% (95% CI: 81.1% to 93.3%). A complete radiological and serum marker response to chemotherapy alone was experienced by 79 men (62%); residual masses post chemotherapy were resected in 39 patients (31%), showing undifferentiated tumour in only six (15%). Of the 127 patients, 23 (18%) failed to respond or developed recurrent disease after BEP; only five of these were successfully salvaged. Bleomycin-induced pneumonitis developed in 13% of cases with one death. Twenty-one men had children following chemotherapy, but semen analysis 12 months or more (median 36 months) after treatment showed azoospermia in 11 out of 54 (20%). Long-term follow-up in an observational study has suggested the possibility of late effects on renal function in patients treated for testicular cancer.⁶ In addition to these adverse effects, several studies indicate an increased risk of second malignancies in patients treated with chemotherapy (or radiotherapy) for testicular cancer.^{7, 8}

Two RCTs have compared BEP with CEB (substituting carboplatin for cisplatin).^{38, 39} Both reported inferior results for carboplatin-based chemotherapy in terms of response and survival. In the MRC trial, 598 patients were randomised between BEP and CEB. Failure-free survival rates at one year were 91% with BEP and 77% with CEB ($p = 0.009$).³⁹ Three year survival rates were 97% and 90% respectively ($p = 0.003$). One study enrolled 54 patients who were randomised between BEP and CEB; the deaths of four patients in the CEB arm compared with one in the BEP arm led to early closure of the trial.³⁸

A third randomised study compared etoposide with either cisplatin or carboplatin in 'good risk' patients and this, too, reported inferior results using carboplatin.³⁷ This multicentre trial randomised 270 patients to receive four cycles of either EP or EC. Thirty-two patients (24%) who received carboplatin experienced an incomplete response or relapse compared with 17 of 134 patients (13%) who received cisplatin ($p = 0.02$). No difference in overall survival was evident ($p = 0.52$). A fourth study in metastatic seminoma compared etoposide/cisplatin (EP) with single agent carboplatin.⁵⁵ In the light of inferior progression-free survival in the carboplatin arm and of the results of

the other studies, this trial was discontinued early by the Data Monitoring Committee, although the difference between the two arms was not statistically significant.⁵⁵ A second RCT has also shown no significant survival difference in patients with metastatic seminoma treated with single agent carboplatin or cisplatin, etoposide and ifosfamide.⁵⁶

Several RCTs have compared regimes that varied only by the inclusion or exclusion of bleomycin. Whilst an ongoing systematic review is in progress, three of the studies have reported inferior results in arms omitting bleomycin.^{31, 33, 34} Another study, also in good prognosis patients, compared three cycles of BEP with four cycles of EP (with a dose etoposide of 500mg/m²) and showed equivalence.³⁶ Overall, the systematic review reports on seven RCTs and 1,549 patients and indicates superior outcomes in bleomycin treated patients despite the risk of serious or fatal lung toxicity.⁶⁹

An alternative approach is to substitute other drugs or other regimes for bleomycin-containing regimes. An RCT in good prognosis patients compared EP (with an etoposide dose of 500mg/m²) with VAB-6 (vinblastine, bleomycin, cisplatin, cyclophosphamide and dactinomycin), a regime believed to be equivalent to BEP. This showed equivalence in terms of response and event-free survival.³⁰ An RCT compared PVB with PVE (substituting etoposide for bleomycin) and reported the regimes to be equivalent.³² This has not been formally tested. Attempts to substitute ifosfamide for bleomycin have been reported in two RCTs, one in good prognosis³⁵ and one in poor prognosis⁵⁰ metastatic germ cell tumours. Both reported equivalent response rates and survival, but greater toxicity in the ifosfamide arms.

Several RCTs have investigated alternative regimes using BEP, particularly in 'poor risk' patients. High dose chemotherapy as a first-line treatment has been evaluated in five RCTs,^{42-45, 57} with two further trials in progress. Two trials have reported a benefit for high dose chemotherapy,^{42, 57} while three have reported no benefit.⁴³⁻⁴⁵ The two trials that showed a benefit compared high dose regimes to PVB. In one of these, the control arm comprised a regime whose cisplatin dose was low by current standards⁴⁴ and where the chemotherapy was cycled four-weekly rather than three-weekly as is now standard. Neither study permits a reliable comparison between high dose chemotherapy and modern BEP.

A schedule of escalating etoposide, ifosfamide and cisplatin with autologous stem cell support has reported encouraging phase II data and has prompted an ongoing EORTC RCT of this regimen compared with BEP.⁷⁰ The difficulty of extrapolating high-dose chemotherapy data to current chemotherapy regimes prompted a matched-pair analysis of cases treated with high-dose and conventional-dose chemotherapy, suggesting a benefit for high dose schedules.⁷¹ However, being non-randomised, there are possible biases in these data and the results of the currently ongoing RCTs are awaited.

Other RCTs in the management of poor prognosis disease have been to alternate PVB with BEP⁴⁹ and to intensify the induction phase of chemotherapy.⁴⁸ In a parallel randomisation in this study, the use of GSCF led to more patients receiving full dose-intensity chemotherapy but this was not associated with an improvement in either failure-free or overall survival.⁴⁶

Preliminary results of an RCT comparing BEP with the combination of cisplatin, doxorubicin, cyclophosphamide, vinblastine and bleomycin (CI:SCA/VB) have been reported, with greater toxicity but no increased efficacy for the CISCA/VB regime.⁵¹

No randomised study has yet demonstrated superior efficacy to BEP for 'poor risk' patients. Other regimes where encouraging phase II data have been reported include C-BOP/BEP.⁴⁷

For patients in the 'good risk' group, RCTs have investigated the feasibility of reducing the amount of treatment without reducing its efficacy. Early randomised studies evaluated the role of maintenance chemotherapy following the induction of remission; three RCTs compared maintenance with no maintenance.^{27, 28, 52} No study demonstrated benefits, but toxicity was increased with maintenance therapy. Two RCTs have compared three and four cycles of BEP, both using etoposide at a dose of 500mg/m². In both studies there were no differences between three and four cycles in terms of relapse-free survival, disease-free survival or progression-free survival.^{40, 41}

There have been no randomised comparisons of the 'U.S.' BEP regime (based on an etoposide dose of 500mg/m² per cycle) with the 'European' BEP regime (based on an etoposide dose of 360mg/m²), but a study comparing three cycles of BEP using etoposide at a dose of 500mg/m², cycled two-weekly, against four cycles of BEP using 120mg/m² cycled three-weekly showed superior overall survival for the shorter, more intensive regime.²⁹ However, the bleomycin dose in the 'European' arm was lower than in the original regime,⁶⁵ as was the case in the MRC CEB study.³⁹ The most recent comparison of three cycles with four cycles of BEP randomised 812 patients in a 2 x 2 factorial design comparing the number of cycles and also a 3-day compared with a 5-day version of the regimes (at equivalent doses). The two-year progression-free survival was 90.4% with three cycles and 89.4% with four cycles. There was no difference in efficacy between the 3-day and the 5-day schedules, but the 3-day schedule was associated with more toxicity.⁴¹

Only one RCT was found in which the sequencing of surgery and chemotherapy was evaluated. In this trial, patients were randomised to initial debulking surgery followed by chemotherapy compared with initial chemotherapy²⁶ and showed no benefit for initial cytoreductive surgery when the chemotherapy was a VAB-6 type regime.

Long-term effects of treatment for testicular cancer, including chemotherapy, have not been extensively studied. A review of sexual functioning, however, suggested significant morbidity after chemotherapy and radiotherapy. This was based on a search which yielded data on 2,775 patients, from 29 retrospective and seven prospective studies.⁵⁸ This study did not give any quality assessment criteria and the statistical methodology was unclear. More recently, long-term effects on renal function after chemotherapy have been suggested.⁶

Conclusion

BEP chemotherapy remains the standard primary treatment option for all patients with metastatic germ cell tumours following orchidectomy, though the schedule may differ according to the patient's prognostic risk category.

Alternatives to BEP do exist and are used in some centres. The toxic and long-term effects of treatment are ill-defined.

e) Radiotherapy and surgery for metastatic disease

Radiotherapy for Stage II seminoma is reported to cure a high proportion of patients. Precise relapse rates are difficult to define, but are of the order of 7% to 20% for stages IIa and IIb and up to 50% for Stage IIc. On this basis, metastatic seminoma of Stage IIc or higher are treated with primary chemotherapy.⁵⁹

The addition of adjuvant carboplatin to radiotherapy has been piloted.⁶⁰

Metastatic seminoma commonly resolves leaving a residual fibrotic mass, which is slow to dissipate. Retrospective analysis from databases submitted to the MRC has suggested that adjuvant radiotherapy is of only limited effectiveness in preventing further relapse in this situation.⁶¹ This study collected retrospective data from 302 patients treated in 10 European centres and represents the best available evidence on this question. In a non-randomised, retrospective comparison of irradiated and non-irradiated patients, the absolute benefit of radiotherapy was a 2.3% reduction in disease progression and is arguably of little clinical significance.⁶¹

Radiotherapy for NSGCT has been little studied following early RCTs in which it appeared to have no place in the management of Stage I and II disease in combination with either surgery (RPLND) or chemotherapy.^{63, 64} Evidence for the effectiveness of radiotherapy in eradicating localised metastatic NSGCT can, however, be inferred from the Danish RCT in Stage I disease.¹⁷ In this study, relapse in the para-aortic nodes was completely prevented by irradiation (compared with 14 relapses in the 150 patients who did not receive radiotherapy). Whether this applies to bulky NSGCT residual masses cannot be determined. The place of radiotherapy in patients with cerebral metastases has been studied in a pooled, European retrospective study.⁶² This study suggested that radiotherapy to the brain had limited impact in patients undergoing treatment for brain metastases at first presentation, but may be an important component of treatment for those relapsing with brain metastases after induction chemotherapy.⁶²

Residual masses are present in up to 50% of patients with NSGCT following chemotherapy.⁶⁵ They contain necrotic tissue, active cancer, differentiated teratoma or a mixture of all three cell types. Observational studies of surgical excision of such masses have confirmed that a proportion of patients in whom active cancer was demonstrated are subsequently cured.^{66, 67} Techniques for such surgical removal may involve combined thoraco-abdominal surgery or other complex procedures.^{66, 67}

Conclusion

Radiotherapy is a standard treatment option for Stage IIa and IIb seminoma. It may have a role in metastatic NSGCT in appropriate patients.

Radiotherapy has little routine place in the management of residual seminomatous masses after chemotherapy. Surgery for residual NSGCT masses may cure some patients with active disease, but is a complex procedure.

Table 6.1: Inguinal surgery and scrotal violation in testicular cancer: systematic review

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Capelouto, 1995. ¹ USA III	To determine the effects of inguinal surgery and scrotal violation in testicular cancer patients and its effects on prognosis.	<p><i>Participants</i> Adults with testicular germ cell carcinoma where violation of the scrotum had occurred.</p> <p><i>Interventions</i> Scrotal violation including open testicular biopsy, trans-scrotal orchidectomy and fine needle aspiration.</p> <p><i>Design</i> Published series (non-randomised)</p>	<p>Local recurrence rate (tumour recurrence in the scrotum or inguinal region, including the superficial nodes).</p> <p>Distant recurrence rate (any other recurrence including the retroperitoneum or recurrence identified by serum markers).</p> <p>Survival.</p>	<p>7 series were identified giving details of 1,182 patients.</p> <p>Mean follow-up ranged from 22.6 months to 116 months.</p> <p>The rate of distant recurrence was not significantly different between inguinal surgery (11.5%) and scrotal violation (12.7%), $p = 0.37$.</p> <p>The rate of local recurrence was low but the difference was statistically significant (0.4% for inguinal violation compared with 2.9% for scrotal violation, $p < 0.001$).</p> <p>Survival rates were not significantly different (91.5% for inguinal violation compared with 92.7% for scrotal violation, $p = 0.33$).</p> <p>The rate of distant recurrence among patients with Stage I disease was not significantly different between inguinal (9.8%) and scrotal violation (12.0%), $p = 0.24$.</p> <p>Respective rates of survival among patients with Stage I disease were 96.1% compared with 98.6% ($p = 0.11$) and local recurrence rates were 0.1% compared with 1.3% ($p = 0.07$).</p> <p><i>Seminoma</i> There was no significant difference between inguinal and scrotal violation for local recurrence rate (0.0% compared with 1.3% $p = 0.15$), distant recurrence rate (5.3% compared with 4.6% $p = 0.15$) or survival rate (95.2% compared with 95.05%, $p > 0.50$).</p> <p><i>NSGCT</i> There was no significant difference between inguinal and scrotal violation for local recurrence rate (1.0% compared with 2.3%), distant recurrence rate (12.6% compared with 4.5%, $p = 0.12$) and survival rate (100% compared with 97.7% $p = 0.34$).</p> <p>Analysing only patients with scrotal violation indicated no significant difference between those receiving local adjuvant therapy and those who did not in terms of local recurrence rate (1.0% compared with 2.3%, $p > 0.50$), survival (100% compared with 97.7%, $p = 0.34$), distant recurrence (12.6% compared with 4.5%, $p = 0.12$).</p>	<p>No search strategy provided or information on databases searched was provided.</p> <p>No RCTs available.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> All published series on testicular carcinoma between 1958 and 1993 selected.</p> <p><i>Inclusion criteria</i> Data series comparing patients with and without scrotal violation.</p> <p>Series which included the three endpoint outcomes.</p> <p><i>Quality assessment</i> Not stated.</p> <p><i>Study details</i> Not given.</p> <p><i>Appropriate synthesis of results</i> Statistical significances compared using the Fleiss method.</p>





Table 6.2: Stage I Seminoma - Optimisation of adjuvant radiotherapy: RCTs

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Aass, 1997. ² Norway II	To evaluate the efficacy and side-effects during radiotherapy of seminoma of prophylactically administered topisetron compared with metoclopramide	<p><i>Participants</i> 23 patients with Stage I seminoma (18 to 70 years).</p> <p><i>Intervention</i> Abdominal radiotherapy (para-aortic and ipsilateral region) 30Gy in 15 fractions over 3 weeks, 2Gy/day.</p> <p>Patients were randomised to oral topisetron 5mg daily (n = 11) or metoclopramide 10mg 3 times daily (n = 12). Drugs were given from day 1 of radiotherapy and throughout the treatment period.</p> <p><i>Design</i> RCT.</p>	Nausea. Emetic episodes. Abdominal pain. Bowel frequency.	<p>Nausea was significantly lower with topisetron compared with metoclopramide (median 0.14 compared with 1.32, p = 0.03). Two patients randomised to topisetron and 9 randomised to receive metoclopramide patients experienced significant nausea (p = 0.01). One patient on topisetron had emetic episodes compared with 6 on metoclopramide (p = 0.07).</p> <p>No difference was seen in the incidence of abdominal pain, bowel motions or diarrhoea.</p>	<p>This study has a small number of patients but statistics based on number of events (i.e. number of vomiting episodes).</p>	<p><i>Randomisation</i> This was a prospective open RCT.</p> <p>Patients kept a diary scoring their experience of nausea and abdominal pain.</p> <p><i>Allocation concealment</i> Not stated. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Mean scores were calculated for nausea, emesis, abdominal pain and bowel motions. Wilcoxon rank test was used to compare differences.</p> <p>Fischer's exact test for distributions.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Fosså, 1999. ⁴ Norway, UK II	To compare relapse rates and toxicities associated with para-aortic strip radiotherapy (PA) and ipsilateral iliac lymph node irradiation (known as a dogleg field (DL)) for Stage I testicular seminoma.	<p><i>Participants</i> 478 patients with testicular pure seminoma were entered in this trial. All had Stage I disease (Royal Marsden Classification), elevated AFP (not HCG), normal abdominal lymphogram/CT scans, Stage T1 to T3 disease and no ipsilateral or scrotal operations.</p> <p><i>Intervention</i> Adjuvant radiotherapy with 30Gy in 15 fraction over 3 weeks.</p> <p><i>Design</i> RCT.</p>	<p>Relapse.</p> <p>Recurrent-free survival.</p> <p>Overall survival.</p> <p>Toxicity.</p> <p>Sperm counts.</p>	<p>The median follow-up was 4.5 years.</p> <p><i>Efficacy</i> 9 patients relapsed in each arm. In 4 patients, all of whom were in the PA arm), pelvic relapse was detected. The 3 year relapse-free survival was 96% (95% CI: 94% to 99%) after PA and 96.6% (95% C: 94% to 99%) after DL. One patient died of disease (PA). Survival at 3 years was 99.9% for PA and 100% for DL radiotherapy.</p> <p><i>Toxicity</i> During radiotherapy, acute toxicity was greater with DL field in terms of nausea/vomiting (p = 0.08), leukopenia (p < 0.0001) and gastrointestinal symptoms (p = 0.13). Sperm counts were significantly higher with PA.</p>		<p><i>Randomisation</i> RCT. Randomisation occurred 8 weeks or fewer from orchidectomy. A total of 236 patients were randomised to PA and 242 to DL.</p> <p><i>Allocation concealment</i> Not stated. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Event-free times were measured from date of randomisation and rates were calculated by Kaplan Meier method; toxicities were compared using χ^2.</p>



Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Jones, 2001. ⁵ UK II	To determine the efficacy and morbidity of two dose schedules of radiotherapy for Stage I seminoma.	<p><i>Participants</i> 625 patients with Stage I seminoma.</p> <p><i>Intervention</i> Patients were randomised within 8 weeks of inguinal orchidectomy to receive either 20Gy in 10 fractions over 2 weeks or 30Gy in 15 fractions over 3 weeks.</p> <p><i>Design</i> RCT.</p>	Relapse-free rate. Morbidity	<p><i>Efficacy</i> At a median follow-up of 37 months, 8 relapses reported in the 30Gy group and 10 in 20Gy group (HR 1.27, 90% CI; 0.58 to 2.8). The difference in the 2 year relapse rates is 0.3%, (90% CI; -1.9% to 2.5%). An additional 393 patients have been randomised to the same doses within a subsequent trial (MRC TE19) of whom 6 (30Gy – 5 patients and 20Gy – 1 patient) have relapsed. A combined analysis of all 1,018 patients from the two trials gave a difference in relapse rates at 2 years of 0.8% in favour of 20Gy.</p> <p><i>Toxicity</i> Significantly more patients on 30Gy reported moderate or severe lethargy 4 weeks after radiotherapy (20% compared with 5%) and an inability to work normally (46% compared with 28%). At 12 weeks the activity in each group was similar.</p>	Large number of patients. In abstract form only.	<p><i>Randomisation</i> RCT.</p> <p><i>Allocation concealment</i> The report did not state the level of allocation concealment. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Hazard rates calculated for relapse rates.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Khoo, 1997. ³ UK II	To evaluate the acute gastro-intestinal morbidity of adjuvant radiotherapy for Stage I seminoma of the testis.	<p><i>Participants</i> Patients with Stage I seminoma.</p> <p><i>Interventions</i> All patients were given para-aortic and ipsilateral pelvic nodal (dog-leg) radiotherapy (RT) as required. 10 patients were allocated to Group A. Patients in this group did not receive anti-emetics. 10 patients were randomised to receive either prophylactic ondansetron (8mg 8-hourly)(Group B). 10 patients were randomised to expectant therapy with metoclopramide (10 to 20mg 8-hourly) (Group C).</p> <p><i>Design</i> Randomised 2 x 2 factorial design.</p>	Acute toxicity.	<p>Nausea, vomiting, diarrhoea and abdominal discomfort were seen in 90%, 80%, 70% and 90%, respectively, of patients not given regular anti-emetics. Anti-emetics were prescribed for 70% of patients and anti-diarrhoeal agents were given to 10% of patients.</p> <p>Overall, nausea, vomiting, diarrhoea and abdominal discomfort seen in 80%, 45%, 60% and 80%, respectively, of patients given anti-emetics (Groups A or B).</p> <p>With ondansetron, less nausea ($p = 0.02$) and vomiting were seen ($p = 0.06$). Anti-emetics in the expectant group gave at least a two-fold reduction of toxicity grade in 86% of patients. Lethargy, anorexia and headaches were observed in all groups.</p>	<p>Small number of patients.</p> <p>Data were collected prospectively by questionnaire.</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Fisher's exact test was used to compare treatment modalities. The Mann Whitney-U test was used to compare patients with or without any level of toxicity.</p>



Table 6.3. Chemotherapy and surveillance in the management of Stage I testicular cancer: primary studies

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Rorth, 1991. ¹⁷ Denmark II	To compare surveillance alone compared with radiotherapy, following orchidectomy in NSGCTs.	<p><i>Participants</i> Stage I NSGCT germ cell cancers according to a modified WHO system (no evidence of disease on CT scan, lymphangiography, urography, chest radiography, tumour markers).</p> <p><i>Intervention</i> After orchidectomy patients were randomised to surveillance or radiotherapy (40Gy in 25 fractions over 5 weeks) to para-aortic and ipsilateral pelvic lymph nodes. Patients followed monthly for 1 year and reducing to , bi- or tri-monthly second year. Follow-up lasted for 5 years after disease-free status was achieved.</p> <p><i>Design</i> Multicentre RCT.</p>	Recurrence-free survival. NED.	<p>150 patients were assessable, 73 on radiotherapy and 77 on surveillance.</p> <p>Relapse occurred in 11 and 23 patients in the radiotherapy and surveillance groups, respectively. Retroperitoneal relapse occurred in the surveillance group only (n = 14).</p> <p>All relapsed patients in the surveillance group are alive without disease (median observation time 67 months).</p> <p>Two patients with relapse in the radiotherapy group died; the rest are alive without disease (median observation 72 months).</p> <p>1 and 4 relapses occurred later than 2 years in the radiotherapy and surveillance groups respectively.</p>		<p><i>Randomisation</i> Multicentre RCT. Patients were stratified according to whether tumour markers were elevated prior to orchidectomy.</p> <p><i>Allocation concealment</i> Randomisation performed by central closed envelope system. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Relapse-free survival plotted by Kaplan-Meier method and log-rank test.</p>

Table 6.4: Chemotherapy for early stage germ cell tumours: Primary Studies

Study Country Grade	Aims	Participants	Outcomes	Results	Comments	Methods
Dearnaley, 1998. ²⁰ UK II	To determine the efficacy of bleomycin, vincristine and cisplatin (BOP) for high risk Stage I NSGCTs.	<i>Participants</i> High risk patients with NSGCTs. <i>Interventions</i> Within 6 weeks of orchidectomy, patients received 2 courses of BOP 14 days apart. BOP consisted of cisplatin (50mg/m ² days 1 and 2), vincristine (1.4mg/m ² days 2 and 8, max 2mg) and bleomycin (30 IU days 2 and 8). <i>Design</i> Prospective pilot study.	Relapse rate. Toxicity.	115 patients were eligible for analysis. 90% received treatment without modification. Reversible alopecia was seen in 20% of patients, declining to 7% at 3 months. During chemotherapy treatment 41% of patients developed WHO grade I neurotoxicity and 5% of patients developed WHO grade II neurotoxicity. 6 months after treatment with chemotherapy had ceased, 22% of patients still had grade I neurotoxicity and 1% of patients had grade II neurotoxicity. No changes in hearing, lung function or fertility was seen at 12 months. Median follow-up was 14 months (range 7 months to 30 months). 2 patients relapsed (at 3 months and 6 months). The 12-month relapse-free rate was 98.3% (95% CI: 93.7% to 99.9%).	In abstract form only.	<i>Randomisation</i> No <i>Allocation concealment</i> Not applicable. <i>Completeness of patient data</i> Yes <i>Appropriate analysis of results</i> Yes
Cullen, 1996. ¹⁹ UK IV	To evaluate the efficacy and long-term toxicity of adjuvant chemotherapy in high risk Stage I NSGCTs of the testis.	<i>Participants</i> Patients with newly diagnosed Stage I NSGCTs of the testis and 50% risk of relapse. <i>Intervention</i> 2 courses of chemotherapy. Cisplatin 100mg/m ² , Bleomycin 30mg weekly x 3. Etoposide 120mg/m ² x3 every 21days.	Toxicity (fertility, lung function and audiometry). Relapse. Survival.	123 patients were recruited from 16 UK centres and 1 Norwegian centre but only 114 patients were eligible. Median follow-up was 4 years. <i>Efficacy</i> 2 relapses were reported. 97% of patients were relapse free at 1 year, 83% were relapse free at 2 years and 67% of patients were relapse free for more than 3 years <i>Short-term toxicity</i> Grade 2 leukopenia 18% Grade 3 leukopenia 3% Grade 2 nausea/ vomiting 26%	This study is a non-randomised phase II trial. Included as it has influenced treatment policies.	<i>Randomisation</i> Non-randomised phase II trial. Analysis of multiple cases at several centres identified by a designated pathologist. <i>Allocation concealment</i> Not applicable. <i>Completeness of patient data</i> Yes <i>Appropriate analysis of results</i> Early termination scheme used.





Study Country Grade	Aims	Participants	Outcomes	Results	Comments	Methods
		<p><i>Design</i> Non-randomised phase II trial.</p>		<p>Grade 3 emesis 27% Sensory neuropathy 11%</p> <p>One death owing to a cerebrovascular accident during treatment.</p> <p><i>Long-term toxicity</i> No significant effect was demonstrated on sperm density. No significant difference were seen between pre- and post-treatment values for forced vital capacity, forced expiratory capacity or total lung capacity.</p> <p>15/16 patients had a decrease in transfer factor coefficient (mean difference was 15%, p = 0.002).</p> <p>Median follow-up of 4 years.</p>		
Read, 1992. ¹⁸ UK VI	To determine the relapse-free rate and histological criteria that predict relapse in Stage I NSGCT on surveillance after orchidectomy.	<p><i>Participants</i> Patients with Stage I NSGCT's.</p> <p><i>Interventions</i> Orchidectomy followed by surveillance.</p> <p><i>Design</i> Prospective study.</p>	Relapse-free rate. Survival.	<p>396 patients were entered in the study; 373 patients were eligible for analysis.</p> <p>The two-year actuarial relapse-free rate after orchidectomy was 75% (95% CI: 71% to 79%). The rate at 5 years was 73%. The relapse rate in patients with 3 or 4 risk factors was 54%.</p> <p>Five patients died of tumour or treatment-related complications. Survival at 5 years was 98%.</p>	Risk factors based on the presence of venous and lymphatic invasion, undifferentiated cells and the absence of yolk sac elements in the primary tumour.	<p><i>Randomisation</i> No.</p> <p><i>Allocation concealment</i> Not applicable.</p> <p><i>Completeness of patient data</i> Yes.</p> <p><i>Appropriate analysis of results</i> Yes</p>

Table 6.5: Chemotherapy for good prognosis germ cell tumours: RCTs

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Bajorin, 1993. ⁵⁷ USA II	Evaluate the efficacy of etoposide and carboplatin (EC) compared with etoposide and cisplatin (EP) in good risk germ cell tumours.	<p><i>Participants</i> 270 patients with good risk germ cell tumours.</p> <p>Good risk was defined according to the Memorial Sloane Kettering Cancer Centre.</p> <p>Included patients had Stage I or II disease. Patients with extra-gonadal disease as well as disease confined to the testes were included. Those with relapsed seminoma after radiotherapy and patients with NSGCT of gonadal origin.</p> <p>265 patients were deemed assessable; 131 were treated with EC and 134 with EP.</p> <p><i>Intervention</i> Randomised to receive 4 cycles of EP or EC.</p> <p>Chemotherapy consisted of 4 cycles of either EP or EC.</p> <p><i>Design</i> RCT.</p>	Complete response. Relapse. Incomplete response. Survival. Toxicity.	<p>115 of 131 patients (88%) achieved complete response (CR) on EC and 121 of 134 patients (90%) on EP ($p = 0.32$).</p> <p>16 patient (12%) relapsed on EC from CR patients compared with 4 patients (3%) on EP.</p> <p>32 (24%) patients on the EC had incomplete response or relapse compared with 17 patients (13%) on the EP regime ($p = 0.02$).</p> <p>At a median follow-up 22.4 months, relapse-free survival was inferior with EC ($p = 0.005$). No difference was seen in the rate of overall survival ($p = 0.52$).</p>	These conclusions are in keeping with other cisplatin compared with carboplatin trials.	<p><i>Randomisation</i> The trial was a group sequential design allowing periodic review of data.</p> <p>It was designed to detect the possibility that carboplatin was inferior to cisplatin.</p> <p><i>Allocation concealment</i> Permuted block concealment. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> 4 interim analyses were performed after 24 patients per arm.</p> <p>The study was designed to have a 93% power to detect a reduction in complete response rate from 90% to 77.7% at 15% significance.</p>
Bokemeyer, 1996. ³⁸ Germany II	To compare a combination regime of carboplatin, etoposide and bleomycin (CEB), with cisplatin, etoposide and bleomycin (PEB) in NSGCTs.	<p><i>Participants</i> Patients with minimal and moderate NSGCTs.</p> <p><i>Intervention</i> PEB was given for 3 cycles on days 1 to 5. Cisplatin was given at a dose of 20mg/m² and etoposide was administered at a dose of 100mg/m². Both drugs were given in short infusions on days 1 to 5. Bleomycin was given as a 30mg per day bolus</p>	Complete response. Relapse rate. Active tumour at resection. Progression-free survival rate.	<p>54 patients were enrolled in the study. 29 patients were randomised to the PEB and 25 patients were randomised to receive CEB chemotherapy.</p> <p><i>Efficacy</i> Complete response rates were similar between the two arms – 81% for the PEB arm and 76% for the CEB arm.</p> <p>Relapse rates greater with CEB 32% compared with 13%.</p> <p>Four patients have died of disease progression on CEB (16%) compared with 1 patient (3%) on PEB.</p>	Trial closed prematurely	<p><i>Randomisation</i> RCT. Patients were stratified according to disease extent (59% with minimal disease).</p> <p><i>Allocation concealment</i> Not stated. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p>





Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
		<p>on days 1, 8 and 15. Treatment was cycled every 3 weeks.</p> <p>CEB was given for 4 cycles and consisted of carboplatin (5mg/mlmin as a short infusion day 1), etoposide (120mg/m² days 1 to 3), bleomycin (30mg days 1, 8 and 15 (omitted on final cycle)).</p> <p><i>Design</i> RCT.</p>		<p>Significantly higher rates of negative events (relapse, tumour at resection, death from disease/therapy) with CEB led to the early termination of trial.</p> <p>At median follow-up of 33 months, negative events analysis was in favour of PEB (p = 0.03).</p>		<p><i>Appropriate analysis of results</i> Survival rates expressed as percentages. The Pearson test was used for comparison between arms.</p>
Bosl, 1988. ³⁰ USA II	To compare the toxicity and efficacy of etoposide and Cisplatin (EP) with the efficacy and toxicity of a combination of Vinblastine, Bleomycin, Cisplatin, Cyclophosphamide and Dactinomycin (VAB-6) in good prognosis germ cell tumours.	<p><i>Participants</i> 164 patients with good prognosis Germ cell tumours.</p> <p>Good prognosis was defined as: pure seminoma or testicular NSGCT with a calculated probability of a complete response of > 0.5.</p> <p>Six patients were ineligible.</p> <p><i>Intervention</i> Three cycles VAB-6: Vinblastine 4.0mg/m² day 1, cyclophosphamide 600mg/m² day 1, Dactinomycin 1.0mg/m² day 1, Bleomycin 30 U day 1, Bleomycin 20 U/m² day 1 to 3, Cisplatin 120mg/m² day 4.</p> <p>Four cycles EP: Etoposide 100mg/m² day 1 to 5, Cisplatin 120mg/m² day.</p> <p><i>Design</i> RCT.</p>	<p>Complete response.</p> <p>Event-free survival.</p> <p>Toxicities.</p> <p>Recurrent-free survival.</p> <p>Overall survival.</p>	<p><i>Efficacy</i> 79 patients (96%) achieved a complete response on VAB-6 and 76 patients (93%) on EP achieved complete response. This difference was non-significant.</p> <p>20% of patients on VAB-6 had active residual disease at operation compared with 8% for EP.</p> <p>The difference in the rates of event-free survival was not significantly.</p> <p><i>Toxicity</i> Toxicity was significantly less with EP</p> <p>Emesis p = 0.06 Mucositis p = 0.09 WBC nadir p = 0.06 Platelet nadir p = 0.01 Magnesium nadir p = 0.001.</p> <p>No deaths occurred.</p> <p>16% in VAB-6 arm had bleomycin removed at second cycle.</p>	<p>Numbers for event-free survival were not stated.</p>	<p><i>Randomisation</i> Yes. Patients were stratified by institution.</p> <p><i>Allocation concealment</i> Randomisation accomplished by use of random permuted block design.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Differences between the arms were evaluated by χ^2, Mann Whitney and Wilcoxon Tests. The Kaplan Meier method used for survival data.</p>
Culine, 1999. ³⁶ France II	To determine whether 3 cycles of bleomycin, etoposide and cisplatin (3 BEP) or 4 cycles of etoposide and cisplatin (4 CEP)	<p><i>Participants</i> 250 patients with good-risk metastatic NSGCTs. 209 eligible patients were randomised to 3 BEP (n = 106) or 4 EP (n = 103).</p> <p>Good risk was defined according to the Institute Gustave Roussy model</p>	<p>Complete response.</p> <p>Incomplete response.</p> <p>Relapse.</p> <p>Overall</p>	<p>6 patients were identified as poor-risk according to the IGCCCG prognostic classification owing to extra-pulmonary visceral metastases.</p> <p>Median follow-up 24 months.</p> <p><i>Efficacy</i> Favourable responses were seen in 98 of 106 patients (92%)</p>	<p>Published as an abstract only.</p> <p>Definition of favourable responses and adverse events were not clearly</p>	<p><i>Randomisation</i> RCT.</p> <p><i>Allocation concealment</i> The level of concealment of allocation was not stated. The report did not state if the</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
	cisplatin (4 EP) are equivalent regimen in non-seminoma germ cell tumours.	<p>based on AFP and HCG levels.</p> <p><i>Intervention</i> 3 BEP consisted of 3 cycles of bleomycin 30 U/week on days 1, 8 and 15, etoposide 100mg/m² /day on days 1 to 5 and cisplatin 20mg/m² /d days 1 to 5 every 3 weeks.</p> <p>4 EP consisted of 4 cycles of the same regime but without the bleomycin.</p> <p><i>Design</i> RCT.</p>	<p>survival.</p> <p>Toxicity.</p>	<p>on 3 BEP treated with 94 of 103 patients (91%) treated with 4 EP arm (p = 0.1).</p> <p>Adverse events occurred in 15 and 19 patients treated with 3 BEP and 4 EP, respectively (p = 0.3).</p> <p>Overall survival was 97% (103 of 106 patients) in the 3 BEP arm and 96% (99 of 103 patients) in the 4 EP arm.</p> <p><i>Toxicity</i> Grade 4 neutropenia was seen in 73% on 3 BEP and 85% on 4 EP, grade 1 cutaneous toxicity 24% compared with 8% and grade 1 neurotoxicity was 14% compared with 5%. No toxic deaths were seen.</p>	stated.	<p>study was blinded.</p> <p><i>Completeness of patient data</i> Not stated.</p> <p><i>Appropriate analysis of results</i> Not stated.</p>
De Wit, 2001. ⁴¹ Netherlands, UK, Belgium II	To compare 3 cycles as against 4 cycles of chemotherapy and a 3-day compared with 5-day schedule, in patients with good risk prognosis germ cell cancer.	<p><i>Participants</i> IGCCC good prognosis patients with germ cell cancer were stratified by histology (NSGCT or seminoma) and hospital. Patients within each stratum were then randomised to one of 4 groups; 3 cycles of BEP (3 BEP) for 3 days, 3 BEP for 5 days, 3 cycles of BEP and one of EP (3 BEP-1 EP) for 3 days or 3 BEP-1 EP for 5 years.</p> <p><i>Intervention</i> Treatment consisted of etoposide 500mg/m², either as 100mg/m² days 1 to 5 (5-day regimen) or 165mg/m² days 1 to 3 (3-day regimen), cisplatin at 20mg/m² days 1 to 5 (5-day regime) or 50mg/m² days 1 and 2 (3-day regimen) for either three or four cycle as well as bleomycin 30mg weekly for 9 weeks (total dose 270mg in 3 or 4 cycles).</p> <p><i>Design</i> RCT.</p>	<p>Progression-free survival (PFS).</p> <p>Overall survival.</p> <p>Response.</p> <p>Toxicity.</p> <p>Quality of life.</p>	<p>812 patients were randomised to 3 BEP (n = 406) or 3 BEP-1 EP (n = 406) and 681 of these were randomised to 3 (n = 333) and 5 day (n = 329) schedules.</p> <p>20 patients were ineligible (2.5%).</p> <p>Histology, marker values and disease extent were well balanced in both treatment arms.</p> <p>Median follow-up was 25 months (93% followed for a minimum of 2 years).</p> <p><i>Efficacy</i> 290 of 397 patients (73.1%) who were treated with 3 cycles achieved a status of NED compared with 296 of 395 patients (74.9%) who were treated with four cycles (p = 0.411).</p> <p>The two-year progression-free survival rate was 90.4% for patients treated with 3 cycles and 89.4% for patients treated with 4 cycles, a difference of -1.0% (80% confidence interval, -3.8% to 1.83%).</p> <p>Equivalence for 3 compared with 4 cycles was claimed (upper bound of confidence interval was less than 5%). The hazard ratio for progression-free survival was 0.93 (80% CI: 0.71 to 1.24).</p> <p>247 patients (74.2%) in the '3-days' arm and 240 (72.6%) in</p>	Significant number of patients were entered into this well conducted trial.	<p><i>Randomisation</i> This was a non-inferiority study using a 2 by 2 factorial design to compare a) 4 cycles of 3 BEP-1 EP) with 3 BEP and 5 days BEP with 3 days BEP.</p> <p><i>Allocation concealment</i> No information was given on the level of allocation concealment.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Analysis was on an intention-to-treat basis.</p> <p>Time-to-event data was calculated by the Kaplan Meier method.</p> <p>Quality of life was also assessed by questionnaire</p>





Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
				<p>the '5-day' arm achieved a NED status ($p = 0.718$).</p> <p>The two-year progression-free survival was 89% (95% CI: 86.3% to 93.0%) for the patients in the '3-day' and 88.8% (95% CI: 85.3% to 92.2%) for the patients in the '5 day' arm (difference -0.9%, 80% CI:-4.1 to +2.2%). Equivalence is claimed between the 3 and 5 day schedules.</p> <p><i>Toxicity</i> Myelotoxicity was more pronounced in the '3-day' schedule (leucopenia $p = 0.014$; thrombocytopenia $p = 0.001$). The frequencies of non-haematological toxicities were similar.</p> <p>No difference in efficacy was seen between 3- and 5-days schedules. Overall quality of life scores favoured 3 cycles ($p = 0.03$).</p>		and compared using χ^2 .
De Wit, 1998. ⁵⁰ Netherlands Belgium II	To investigate the efficacy and toxicity of induction chemotherapy containing or not containing bleomycin in intermediate prognosis testicular cancer.	<p><i>Participants</i> 84 patients with metastatic testicular NSGCT were randomised to receive 4 cycles of BEP (n = 41) or 4 cycles of VIP (n = 46).</p> <p><i>Intervention</i> BEP consisted of Bleomycin 30mg day 1 weekly for 12 cycles, Etoposide 120mg/m² days 1, 3 & 5 every 3 weeks and Cisplatin 20mg/m² days 1 to 5 every 3 weeks.</p> <p>VIP consisted of cisplatin 20mg/m² days 1 to 5 every 3 weeks, etoposide 120mg/m² days 1, 3 & 5 every 3 weeks, ifosfamide 1.2 g/m² days 1 to 5 every 3 weeks.</p> <p><i>Design</i> RCT.</p>	Complete response. NED. Progression-free survival. Recurrence-free survival. Overall survival.	<p>Median follow-up was 7.7 years.</p> <p>Complete response rates were similar (74% for VIP compared with 79% for BEP, $p = 0.62$).</p> <p>Disease-free status was achieved in 80% of patients on VIP and 82% of patients on BEP ($p = 0.99$).</p> <p>There was no difference in relapse figures between VIP (11%) and BEP (18%) or five year progression-free survival for VIP (85%) and BEP (83%).</p> <p>The VIP regimen was more myelosuppressive ($p < 0.001$).</p> <p>Two patients in the BEP arm died of cancer (5%) and 1 patient on the VIP arm died of a pulmonary embolism (2%).</p>	Small number of patients.	<p><i>Randomisation</i> RCT. Patients stratified by institute.</p> <p><i>Allocation concealment</i> Not stated. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Response rates and frequency of toxicities were compared using Fischer's Exact test.</p> <p>Dose intensities were compared using Wilcoxon rank-sum and survival analysis calculated by Kaplan-Meier.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
De Wit, 1997. ³⁴ European co-operative group. II	To compare the efficacy of Etoposide and Cisplatin (EP) compared with Bleomycin, Etoposide and Cisplatin (BEP) chemotherapy in patients with good prognosis metastatic NSGCT testicular cancer.	<p><i>Participants</i> Patients with good prognosis NSGCT testicular cancer. No previous radiotherapy or chemotherapy.</p> <p><i>Intervention</i> Four cycles of BEP or four cycles of EP. 20mg/m² cisplatin intravenously on days 1 to 5 every three weeks and etoposide 120mg/m² IV on days 3 and 5 every 3 weeks, with or without bleomycin 30mg weekly for 12 weeks.</p> <p><i>Design</i> RCT.</p>	Response rate. Toxicity. Time to Progression. Survival. NED	<p>419 patients entered but, of these, 395 patients were eligible. 200 patients were randomised to the BEP arm and 195 patients were randomised to the EP arm. Median follow-up was 7.3 years.</p> <p><i>Efficacy</i> The complete response rate was 95% for the BEP arm and 87% for the EP arm (p = 0.276). 4% of patients in each arm relapsed. There was no significant difference in the time to progression for patients treated with BEP compared with patients treated with EP (HR 1.70 95% CI: 0.85 to 3.39, p = 0.136, intention to treat). No significant difference was demonstrated in overall survival (HR 1.67 95%CI: 0.68 to 4.11, p = 0.262 intention to treat). Unfavourable treatment outcomes occurred in the cases of 20 patients treated with EP (10%) and 12 patients treated with BEP (6%).</p> <p><i>Toxicity</i> Acute and late neurotoxicity and pulmonary toxicity were significantly more marked in patients in BEP arm (p < 0.001). Raynaud's syndrome occurred only in patients who received BEP (p < 0.001). Post chemotherapy surgery was performed on 28% and 36% of patients in the BEP and EP arms respectively. BEP related mortality was 3% (4 of malignant disease, 2 of Bleomycin toxicity and 1 unknown) and EP related mortality was 6% (8 of malignant disease, 1 of CVD, 3 others).</p> <p><i>Secondary malignancies</i> BEP arm 1.5% (n = 3). EP arm 0.5% (n = 1).</p>	The definition of good prognosis which was used was that of the MRC/EORTC criteria (1985, 1987). Unfavourable treatment outcomes included incomplete response or progression during treatment.	<p><i>Randomisation</i> Patients randomised to receive four cycles of EP or BEP.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Intention to treat analysis was used. Response rates in treatment regimens were compared using the standard χ^2 test, Fischer's exact test and the Wilcoxon rank sum test used. Time to progression and duration of survival curves calculated using Kaplan Meier method and log rank test.</p>





Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Einhorn, 1989. ⁴⁰ USA II	To compare 4 courses of cisplatin, etoposide and bleomycin (PEB) over 12 weeks with 3 courses of the same combination of drugs over 9 weeks.	<p><i>Participants</i> 184 men with minimal (107 patients) or moderate (77 patients) disseminated germ cell tumours.</p> <p><i>Intervention</i> Cisplatin – 2mg/m²/day x 5 every 3 weeks. Etoposide – 10mg/m²/d x5 every 3 weeks. Bleomycin – 30 U/wk.</p> <p>Patients were randomised to receive the regime for 4 cycles over 12 weeks (96 patients) or 3 cycles over 9 weeks (88 patients).</p> <p><i>Design</i> RCT.</p>	Complete response. NED. Relapse rate. Overall survival	Disease-free status was achieved in 88 patients (98%) on 4 cycles and 93 patients (97%) on 3 cycles. Five patients have relapsed on each arm. Overall survival was 93% on 3 cycles and 97% on 4 cycles.	No toxicity data presented.	<p><i>Randomisation</i> This was an RCT designed to show a 10% difference in response rates between three and four course regimens, which was assumed <i>a priori</i> to be 90%. The sample size of 97 patients was designed to detect a greater difference in a test of size 0.01 with the method of Makuch and Simon.</p> <p><i>Allocation concealment</i> Randomisation by telephone. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>
Einhorn 1981. ²⁷ USA II	To determine the value of maintenance therapy in disseminated testicular cancer following complete remission by induction chemotherapy or cytoreductive surgery.	<p><i>Participants</i> Patients with disseminated germ cell tumours were entered. The mean age of patients was 26 years (range 14 to 72). Embryonal carcinoma was the most common histology (51%), teratoma (35%), seminoma (9%), pure chorionocarcinoma (2%). 70% of patients had advanced disease (more than 5cm³ tumour burden).</p> <p><i>Intervention</i> Patients were randomised to 4 courses of induction chemotherapy with either PVB or PVBD chemotherapy. PVB consisted of cisplatin,</p>	Response. Disease-free status. Toxicity. Relapse rate.	184 patients were enrolled and 171 patients were deemed evaluable. 87 patients were randomised to receive PVB chemotherapy and 84 patients were randomised to receive PVBD chemotherapy. Of 113 patients who achieved disease-free status and were entered into a second randomisation procedure, 58 patients were randomised to maintenance chemotherapy and 55 patients were randomised not to receive maintenance therapy. <i>Efficacy</i> Complete remission was achieved in 56 patients treated with PVB (64%) and 57 patients (68%) treated with PVBD. Disease-free status was achieved in 10 patients (11%) treated with PVB and 9 patients (11%) treated with PVBD. The relapse rate on vinblastine maintenance therapy was 9% while the relapse rate for patients with no maintenance	Unclear of doses and schedules.	<p><i>Randomisation</i> Patients were centrally randomised, based on uniform variable generated by SAS software. Patients were stratified according to the tumour surface area. The number of patients in each regime was force-balanced in groups of 4.</p> <p><i>Allocation concealment</i> Yes</p> <p><i>Completeness of patient data</i> Yes</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
		<p>vinblastine and bleomycin.</p> <p>PVBD consisted of cisplatin, vinblastine, bleomycin and doxorubicin.</p> <p>113 patients with complete response/disease-free after surgery for residual mass were further randomised to vinblastine maintenance (3mg/kg every 4 weeks or no therapy).</p> <p><i>Design</i> RCT.</p>		<p>therapy was 7%. Disease-free status was achieved in 56 patients (97%) treated with maintenance therapy and 59 patients (96%) who were not treated with maintenance therapy.</p> <p><i>Toxicity</i> Toxicity was similar although more nausea and alopecia were seen in patients who had been treated with PVBD. Seven treatment-related deaths occurred (4 from bleomycin lung fibrosis).</p>		<p><i>Appropriate analysis of the results</i> Survival curves were plotted using the Kaplan-Meier technique and were compared using the generalised Wilcoxon method.</p>
Horwich, 1997. ³⁹ UK, Belgium II	To evaluate the efficacy of carboplatin, etoposide and bleomycin (CEB) compared with cisplatin, etoposide and bleomycin (BEP) as first line therapy for good risk NSGCTs.	<p><i>Participants</i> 598 good-prognosis patients with metastatic NSGCTs were randomised to receive 4 cycles of either BEP (n = 300) or CEB (n = 298).</p> <p><i>Intervention</i> BEP – bleomycin 30 U on day 2, etoposide 120mg/m² on days 1, 2 and 3, cisplatin 20mg/m² per day on days 1 to 5 or 50mg/m² on days 1 and 2. CEB – etoposide and bleomycin were given as above. Cisplatin was given at a dose calculated to achieve 5mg/mlmin.</p> <p><i>Design</i> RCT.</p>	<p>Complete response.</p> <p>Treatment failures.</p> <p>Failure-free survival.</p> <p>Overall survival.</p> <p>Toxicity.</p>	<p>Median follow-up of surviving patients was 3 years (80% monitored for at least 2 years).</p> <p><i>Efficacy</i> Complete response (on chemotherapy alone or with resection of a residual post-chemotherapy mass) was seen in 253 of 268 patients (94%) on BEP and 227 of 260 patients (87%) on CEB. The hazard ratio for failure-free survival was 2.75 (95%CI: 1.88 to 4.03).</p> <p>There were 30 treatment failures in 300 patients on BEP and 79 in 298 patients on CEB (p < 0.001). Failure-free survival rates at 1 year were 91% for BEP and 77% and CEB respectively (p = 0.009).</p> <p>10 deaths were reported in patients allocated BEP and 27 in patients allocated to CEB (p = 0.003). Three year survival rates were 97% for BEP and 90% for CEB.</p> <p><i>Toxicities</i> Thrombocytopenia was more pronounced with CEB (p < 0.001).</p>	Good prognosis as defined by MRC (1985)	<p><i>Randomisation</i> RCT. Designed as an equivalence trial.</p> <p><i>Allocation concealment</i> Patients were randomised via MRC-CTO Cambridge and EORTC Brussels.</p> <p>The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Kaplan-Meier used for survival curves and compared with the log-rank test.</p>





Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods										
Levi, 1993. ³¹ Australia, New Zealand II	To compare cisplatin and vinblastine with and without bleomycin in good prognosis germ cell patients.	<p><i>Participants</i> Patients with good prognosis (tumours < 10 cm, no cerebral, bone or hepatic metastases). Germ cell tumours including pure seminoma and pure choriocarcinoma were entered. All had inoperable disease and had not received prior chemotherapy.</p> <p><i>Intervention</i> Randomised to receive cisplatin and vincristine (PV) or cisplatin, vincristine and bleomycin (PVB). Cisplatin 100mg/m² day 1 in a 2 hour I.V. infusion. Vincristine 6mg/m² on days 1 and 21. PV every 3 weeks. Bleomycin 30mg IM on day 1, weekly (maximum of 12 weeks).</p> <p><i>Design</i> RCT.</p>	Complete response. NED. Toxicity. Overall survival. Failure-free survival.	<p>222 patients were enrolled in the study; 218 patients were assessable. Of these 108 were randomised to PV and 110 to PVB.</p> <p>There was a 15% death rate on PV and a 5% rate with PVB (p = 0.02). However, toxicity related deaths were more common among patients randomised to the PVB (p = 0.06).</p> <p><i>Efficacy</i> 89% of patients treated with PV and 94% of patients treated for PVB achieved complete response and NED.(p = 0.29).</p> <p>At four year follow-up, 7% of patients have relapsed on PV and 5% on PVB (p = 0.06).</p> <p>5 patients in each arm had successful salvage surgery.</p> <p><i>Toxicity</i> Patients receiving PVB had more toxicity than those receiving PV.</p> <table border="0"> <tr> <td>Alopecia</td> <td>75% and 58%, p = 0.005</td> </tr> <tr> <td>Renal</td> <td>28% and 18%, p = 0.03</td> </tr> <tr> <td>Pulmonary</td> <td>34% and 0%, p < 0.001.</td> </tr> </table> <p>Haematological toxicities were also greater with PV</p> <table border="0"> <tr> <td>WBC nadirs</td> <td>p = 0.04,</td> </tr> <tr> <td>Thrombocytopenia</td> <td>p = 0.04, Haemoglobin p = 0.004.</td> </tr> </table>	Alopecia	75% and 58%, p = 0.005	Renal	28% and 18%, p = 0.03	Pulmonary	34% and 0%, p < 0.001.	WBC nadirs	p = 0.04,	Thrombocytopenia	p = 0.04, Haemoglobin p = 0.004.		<p><i>Randomisation</i> RCT. Patients were stratified according to extent of disease.</p> <p><i>Allocation concealment</i> Randomised by central random number system. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Response rates used to determine efficacy. The Wilcoxon test was used to analyse toxicity data. Overall, cause-specific and failure-free survival by Kaplan-Meier method.</p>
Alopecia	75% and 58%, p = 0.005															
Renal	28% and 18%, p = 0.03															
Pulmonary	34% and 0%, p < 0.001.															
WBC nadirs	p = 0.04,															
Thrombocytopenia	p = 0.04, Haemoglobin p = 0.004.															

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Loeher, 1995. ³³ USA II	To determine whether 3 cycles of cisplatin and etoposide is more effective than 3 cycles of cisplatin, etoposide and bleomycin in disseminated germ cell tumours.	<p><i>Participants</i> Patients with good risk (on Indiana staging) disease were entered. Only patients with no prior chemotherapy were enrolled. No age or performance status restrictions were applied.</p> <p><i>Intervention</i> Patients randomised to receive either PVP-16, consisting of cisplatin (20mg/m² days 1 to 5) and etoposide (100mg/m² on days 1 to 5) or PVP-16B consisting of the same drugs at the same doses with the addition of bleomycin (30U per week for 9 weeks). 3 cycles of chemotherapy were given over 9 weeks. Patients with residual disease underwent surgical resection. An additional 2 cycles was given if the disease persisted.</p> <p><i>Design</i> RCT.</p>	Complete response. Disease-free survival. Treatment failure. Relapse. Overall survival. Failure-free survival.	<p>178 patients were enrolled in the study; of these, 171 patients were assessable. 85 patients were randomised to receive PVP-16 and 86 patients were randomised to receive PVP-16B.</p> <p><i>Efficacy</i> 66 of 86 patients (77%) achieved complete remission on chemotherapy alone (PVP-16B) compared with 60 of 85 (71%) for PVP-16. An additional 15 patients in each arm were rendered disease-free following resection. Overall disease-free status was achieved in 8 of 86 patients (94%) on PVP-16B and 75 of 85 (88%) on PVP-16. There was a significant difference in adverse treatment outcomes (treatment failure, drug related mortality/intolerance, relapse). 15 patients (17%) for PVP-16B and 32 patients (38%) for PVP-16 experienced such adverse treatment outcomes (p = 0.004). PVP-16 was inferior to PVP-16B for time to treatment failure; 69% of patients and 86% of patients respectively were alive and disease-free at 3 years (p = 0.01). 4 deaths seen on PVP-16B and 14 on PVP-16. Overall survival rates at 3 years 95% and 86% (p = 0.01).</p> <p><i>Toxicities</i> Severe non-haematological toxicities were similar in both arms – 8% and 9% for PVP16B and PVP16, respectively. Mucositis only occurred in PVP-16B. Grade 4 myelosuppression greater with PVP-16B (p = 0.06). One drug-related death was seen on PVP-16B.</p>		<p><i>Randomisation</i> Randomised prospective trial.</p> <p><i>Allocation concealment</i> Randomly assigned by telephone. The report did not state if the study was blinded.</p> <p><i>Completeness of patients data</i> Yes</p> <p><i>Appropriate analysis of results</i> Interim analysis was conducted using the Lan and DeMets method and the O'Brien-Fleming boundary method. Categorical data (response) analysed by Fischer's exact test. Survival and time-to-failure data were analysed by the log-rank and Cox proportional hazards models. Plots using Kaplan Meier method were calculated.</p>





Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Nichols, 1998. ⁵⁵ USA II	To compare BEP (Bleomycin, Etoposide, Cisplatin) with VIP (Etoposide, Ifosphomide and Cisplatin) as primary therapy for advanced germ cell tumours.	<p><i>Participants</i> 304 men with disseminated germ cell tumour.</p> <p><i>Intervention</i> Patients were randomised to BEP or VIP. BEP consisted of etoposide 100mg/m² day 1 to 5, bleomycin 30U IV weekly for 12 weeks, cisplatin 20mg/m² days 1 to 5. VIP consisted of etoposide 75mg/m² days 1 to 5, ifosfamide 1.2g/m² days 1 to 5 (mesna given). 34 patients received G-CSF equal distribution in both arms. Each regimen was given every 3 weeks for 4 cycles.</p> <p><i>Design</i> RCT.</p>	Complete response. NED. Overall. Survival. Failure free survival. Toxicity.	<p>286 assessable patients received either BEP (141) or VIP (145).</p> <p>Complete responses were seen in 31% of patients treated with BEP and 37% of patients treated with VIP.</p> <p>NED was achieved among patients with Teratoma by 11% of patients treated with BEP and 10% of patients treated with VIP.</p> <p>NED was achieved among patients with carcinoma by 1% of patients treated with BEP and 6% of patients treated with VIP.</p> <p>Partial response was achieved by 31% of patients treated with BEP and by 22% of patients treated with VIP.</p> <p>At two years post treatment, 60% of patients treated with BEP had not experienced treatment failure while 64% of patients treated with VIP had not failed at that time (p = 0.29).</p> <p>No difference in overall survival was demonstrated (p = 0.78).</p> <p>Patients who were treated with VIP experienced higher haematological toxicity (p < 0.001).</p> <p>5 deaths of patients treated with VIP and 6 of patients treated with BEP occurred.</p>	No evidence that VIP is superior to BEP.	<p><i>Randomisation</i> RCT. Patients were stratified by co-operative group. Randomisation was by permuted block strategy. The trial design gave a greater than 83% power to detect a 17.5% difference.</p> <p><i>Allocation concealment</i> The level of concealment of allocation was not stated. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Kaplan Meier method used for survival data and compared with log rank. Logistic regression and proportional hazards were calculated.</p>
Stoter 1986. ⁵² Netherlands II	To compare induction chemotherapy with two doses of vinblastine in combination with cisplatin and bleomycin and then to compare no therapy with maintenance to prevent relapse in NSGCT testicular cancer.	<p><i>Participants</i> 214 patients with disseminated NSGCT Stage IIb or higher (Royal Marsden Classification). Patients with persistently high markers.</p> <p><i>Interventions</i> All patients received induction chemo with cisplatin (20mg/m² days 1 to 5 every 3 weeks) and bleomycin (30mg IV weekly). In combination with this regime patients were randomised to high dose vinblastine or low dose vinblastine.</p>	Response. Disease progression. Relapse rate. Survival. Toxicity.	<p>214 patients were entered into the first randomisation. Of these 98 patients were randomised to Group 1 and 116 patients were randomised to Group 2.</p> <p>Of 60 patients who were entered into the second randomisation, 28 patients were allocated to Arm A and 32 patients were allocated to Arm B.</p> <p>A parallel (non-randomised) study enrolled 25 patients (Group 3).</p> <p><i>Efficacy</i> 68% of patients in Group 1, 71% of patients in Group 2 and 69% of patients in Group 3 had complete responses to therapy. Sub-analysis showed patients with low and high volume disease to have equivalent complete response rates.</p>	Considerable attrition on maintenance arm. From 32 patients who were randomised to receive maintenance therapy, only 10 completed 1 year.	<p><i>Randomisation</i> Muticentre RCT.</p> <p><i>Allocation concealment</i> Randomisation was carried out centrally.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Response rates were compared using χ^2. Survival and progression curves were computed using the Kaplan-</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
	testicular cancer.	<p>High dose vinblastine was administered at a dose of 0.2mg/kg/day.</p> <p>Low dose vinblastine was administered at a dose of 0.15mg/kg on days 1 and 2 every 3 weeks. 4 cycles of induction chemotherapy were given.</p> <p>For slow responders (markers fall slowly), 2 further cycles were administered – cisplatin (50mg/m²) and vincristine (0.2mg/kg days 1 and 2).</p> <p>Complete responders were further randomised to no further therapy (Arm A) or maintenance therapy with cisplatin (50mg/m² every 6 weeks) and vincristine (0.2mg/kg every 3 weeks for 1 year) (Arm B).</p> <p>A separate Group 3. (non-randomised) received vincristine (0.15mg/kg), cisplatin and bleomycin.</p> <p><i>Design</i> RCT.</p>		<p>22% of patients in Group 1, 21% of patients in Group 2 and 19% of patients in Group 3 developed progressive disease.</p> <p>10 patients relapsed. 7 patients who relapsed had been treated in Group 1, 2 patients were treated in Group 2 and the remaining patient had been treated in Group 3.</p> <p>The mean survival among all patients at 3 years was 80%. There were no significant differences between the three groups.</p> <p>93% of patients had complete responses to therapy.</p> <p>5 of 7 patients who died had been treated in Group 1 (p = 0.13). Patients with a low volume of disease had a significantly longer survival (p = 0.05) than those with a higher volume of disease.</p> <p>22 patients in Arm A were lost to follow-up. 1 patient had progressive disease and 11 patients developed leukopenia. Of those who were not treated with maintenance therapy, one patient died.</p> <p><i>Toxicity</i> Less leukopenia was experienced by patients in Group 2 (13%) than in the non-randomised Group 3 (29%) (p = 0.01).</p>		Meier method and were compared with log-rank testing.
Toner, 2001. ²⁹ Australia, New Zealand II	A comparison of two BEP regimes for men with good prognosis germ cell tumours.	<p><i>Participants</i> 166 patients with histologically confirmed germ cell tumour (seminoma or NSGCT).</p> <p><i>Intervention</i> Regimen A consisted of 3 cycles of BEP (bleomycin 30kU days 1, 8, 15, etoposide 100mg/m² days 1 to 5, cisplatin 20mg/m² days 1 to 5).</p> <p>Regimen B consisted of 4 cycles of BEP (bleomycin 30kU day 1, etoposide 120mg/m² days 1 to 3,</p>	Complete response. Overall survival.	<p>Median follow-up was 33 months.</p> <p>March 2000, recruitment suspended owing to superior survival for regimen A.</p> <p><i>Survival</i> Overall survival was superior with regimen A. There were 3 deaths in patients treated with Regimen A and 13 in patients treated with Regimen B (HR = 0.22, 95% CI: = 0.06 to 0.77, p = 0.008).</p> <p><i>Mortality</i> Of these deaths, one patient treated with Regimen A died from cancer and 9 patients treated with Regimen B died</p>		<p><i>Randomisation</i> Multicentre RCT.</p> <p><i>Allocation concealment</i> Central telephone randomisation stratified by institution and tumour histology using a balanced algorithm.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of</i></p>





Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
		<p>cisplatin 100mg/m² day 1). Both regimens were cycled every 21 days.</p> <p><i>Design</i> Multicentre RCT.</p>		<p>from cancer. 2 treatment-related deaths resulted from Regimen A and 2 treatment-related deaths resulted from Regimen B.</p> <p><i>Response to treatment</i> A satisfactory response was reported for 87% of patients. No difference was demonstrated between the two treatments.</p> <p>Fewer patients in Regimen A relapsed.</p> <p>Differences in failure-free survival or progression-free survival did not reach statistical significance.</p>		<p><i>results</i> Intention to treat analysis used. Kaplan Meier curves, Cox proportional hazard model and 95% CI calculated.</p>
<p>Weissbach, 1991.²³ Germany II</p>	<p>To compare 2 with 4 courses of cisplatin, vinblastine and bleomycin in NSGCT testicular tumours.</p>	<p><i>Participants</i> Following orchidectomy, 255 patients with metastatic Stage II NSGCT testis tumours were entered. All patients had radical retroperitoneal lymph node dissection (RPLND).</p> <p><i>Intervention</i> Patients were randomised to Arm 1 (2 courses of cisplatin, vinblastine and bleomycin) or 4 course of the same regimen. Courses were given every 21 to 28 days.</p> <p>Cisplatin 20mg/m² days 1 to 5, Vinblastine 6mg/m² days 1 and 2, Bleomycin 12mg/m² days 1 to 5. 5 patients had etoposide instead of vinblastine.</p> <p><i>Design</i> RCT.</p>	<p>Progression-free survival. NED. Disease-specific survival. Recurrence-free survival.</p>	<p>114 patients received 2 courses and 111 patients received 4 courses.</p> <p><i>Efficacy</i> In Arm 1, 6 patients relapsed compared to 1 relapse in Arm 2 (p = 0.75). Survival was 100% in Arm 1 and 97% in Arm 2 (no probability was cited).</p> <p><i>Toxicity</i> Toxicities were not significantly different between arms.</p>		<p><i>Randomisation</i> RCT.</p> <p><i>Allocation concealment</i> Not stated. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> The disease-free interval was calculated according to the Kaplan-Meier method. Differences between the arms was calculated with the Wilcoxon test.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Williams, 1987. ²¹ USA II	To compare adjuvant chemotherapy with surveillance in pathological Stage II testicular cancer.	<p><i>Participants</i> 213 patients with Stage II testicular cancer were included. Patients were initially treated with orchidectomy followed by radical retroperitoneal lymph node dissection (RPLN).</p> <p><i>Intervention</i> Chemotherapy or observation. Chemotherapy consisted of one of two regimes; cisplatin (20mg/m² days 1 to 5), vinblastine (0.15mg/m² days 1 and 2), bleomycin (30U weekly x 4) or cisplatin(120mg/m² day 7), vinblastine(4mg/m² on day 1), bleomycin (30U bolus and 15U/m² on days 1 to 6), cyclophosphamide (600mg/m² day 1) and dactinomycin (1mg/m² day 1). Chemotherapy was given at relapse for patients in the observation arm.</p> <p><i>Design</i> RCT.</p>	Recurrence. Overall survival.	<p>98 patients were randomised to observation and 97 to 2 cycles of chemotherapy. The median follow-up was 4 years. 6 of 97 patients (6%) on adjuvant chemotherapy had tumour recurrence compared with 48 of 98 patients (48%) on observation (p < 0.001). Deaths from all causes were 3 for chemotherapy and 6 for observation. There was no difference in overall survival.</p>	The results of this study attest to efficacy of chemotherapy at relapse.	<p><i>Randomisation</i> RCT.</p> <p><i>Allocation concealment</i> The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> <i>Appropriate analysis of results</i> Categorical variables compared by χ^2. Relapse-free interval assessed by log-rank.</p>



Table 6.6. Chemotherapy for metastatic, poor prognosis germ cell tumours: RCTs

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Chevreau, 1993. ⁴⁵ France II	To investigate the role of high dose chemotherapy with autologous bone marrow transplantation (AuBMT) in first line treatment for poor risk germ cell tumours.	<p><i>Participants</i> 115 non pre-treated patients with poor risk, metastatic, NSGCTs of either testicular or extra-gonadal origin.</p> <p><i>Interventions</i> Arm A consisted of vinblastine (0.2mg/kg day 1), etoposide (100mg/m² days 1 to 5), cisplatin (40mg/m² days 1 to 5) and bleomycin (30mg weekly). Three or four courses were administered every 3 weeks.</p> <p>Arm B consisted of identical doses of vinblastine, etoposide and cisplatin but bleomycin was administered at a dose of 20mg/day on days 1 to 5, then 15mg weekly on days 8, 15. 2 cycles were given at 4 weekly intervals then one cycle of the high dose regimen (cisplatin 40mg/m²/day and etoposide 350mg/m²/day, days 1 to 5, cyclophosphamide 1,600mg/m²/day days 2 to 5) with AuBMT (re-infused on day 8).</p> <p><i>Design</i> RCT.</p>	Relapse and overall survival.	<p>57 patients received Arm A and 57 patients were treated with Arm B.</p> <p><i>Efficacy</i> 23 patients did not complete the treatment (7 of these patients were being treated according to the Arm A protocol and 16 of these patients were treated according to the Arm B protocol).</p> <p>After 2 cycles, markers were normalised in 6 of 57 patients (Arm A) and 12 of 57 patients (Arm B).</p> <p>After completion of the treatment, there were 33 complete responses among Arm A patients (58%) and 24 complete responses among Arm B patients (42%) (p = 0.11).</p> <p>Relapse after complete response status was achieved was more common in patients in Arm B (12 patients) than patients in Arm A (6 patients).</p> <p>The two-year overall survival rate was 80% for patients treated according to the Arm A protocol and 60% for patients in Arm B (log rank p = 0.08).</p> <p><i>Toxicity</i> Grade 4 leucopenia was less common in patients treated by the Arm A protocol (13%) than in patients treated by the Arm B protocol (22%).</p> <p>Grade 3 to 4 mucositis was also less common in patients treated by the Arm A protocol (13%) than in patients treated by the Arm B protocol (22%) 13% and 22%.</p> <p>Decreased renal function was less common in patients treated by the Arm A protocol (7%) than in patients treated by the Arm B protocol (8%).</p>	<p>Poor risk patients had a calculated probability of a complete response of < 0.7 according to IGR prognostic model.</p> <p>No p value was given for relapse rates.</p>	<p><i>Randomisation</i> RCT.</p> <p><i>Allocation concealment</i> The level of allocation concealment was not stated. The report did not state if the study was blinded..</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Survival analysis not stated but log rank test used to compare groups.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
De Wit, 1995. ⁴⁹ Netherlands, UK, Belgium II	To compare alternating cycles of induction chemotherapy of PVB/BEP with BEP alone in poor prognosis testicular cancer.	<p><i>Participants</i> 250 patients with poor prognosis NSGCT were randomised to receive either 4 cycles of alternating PVB/BEP (n = 125) or 4 cycles of BEP (n = 125). 234 were eligible for analysis.</p> <p><i>Intervention</i> BEP consisted of cisplatin (20mg/m² days 1 to 5 every 3 weeks), etoposide (120mg/m² days 1, 3 & 5 every 3 weeks) and bleomycin (30mg day 2 weekly for 12 weeks).</p> <p>PVB consisted of cisplatin and bleomycin as above but with vinblastine (0.15mg/kg days 1 and 2 every 3 weeks) in substitution for etoposide on alternate cycles.</p> <p><i>Design</i> RCT.</p>	<p>Complete response.</p> <p>Relapse rate.</p> <p>Time to progression.</p> <p>Progression-free survival.</p> <p>Toxicity.</p>	<p><i>Efficacy</i> There was no difference in complete response rates. The response rate for the alternating regime was 76% while that of the BEP only regime was 72% (p = 0.58).</p> <p>At an average follow-up of 6 years, there was no significant difference in the rates of relapse from complete response – 16% for the BEP only regime and 12% the combination protocol (p = 0.50).</p> <p>There was no significant difference in time to progression (p = 0.27) or overall survival (p = 0.32). The progression-free survival rate was 80% in both arms.</p> <p><i>Toxicity</i> PVB/BEP was significantly more myelosuppressive in terms of leucopenia (p < 0.001), leucocytopenic fever (p < 0.006) and platelets below 25 x 10⁹/l (p = 0.001). PVB/BEP was significantly more neurotoxic than BEP with an incidence rate of 47% compared with 25% (p = 0.001).</p>	<p>Poor prognosis was defined as the presence of a lymph node metastases of greater than 5 cm dimension, the presence of more than 4 lung metastases, any lung metastases of greater than 2 cm dimension, haematogenic spread outside the lungs (e.g. liver or bone), HCG levels above 10,000IU/l or αFP levels above 1,000IU/l</p>	<p><i>Randomisation</i> RCT.</p> <p><i>Allocation concealment</i> The report did not state the level of allocation concealment. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Time to progression and the duration of survival was computed by the Kaplan-Meier method.</p> <p>The χ^2 test was used for the comparison of toxicity.</p>



Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Fosså, 1998. ⁴⁶ Norway, UK, Belgium, The Netherlands II	<p>To assess the effect of filgrastim (a granulocyte colony stimulating factor or <i>G-CSF</i>) on the proportion of patients who receive full dose-intensity combination chemotherapy and on the toxicity associated with BOP/VIP-B or BEP/EP.</p> <p>To determine the effect of filgrastim on failure-free and overall survival.</p>	<p><i>Participants</i> In the sub-protocol randomisation 263 patients with poor-prognoses were to receive or not receive filgrastim following each cycle of chemotherapy.</p> <p><i>Intervention</i> Filgrastim was administered once daily at a dose of 5 µg/kg subcutaneously. During each BEP, EP or VIP-B cycle filgrastim was given on days 6 to 19 (14 days) and days on days 3 to 9 (7 days) during each BOP cycle.</p> <p><i>Design</i> RCT.</p>	<p>Failure-free survival.</p> <p>Overall survival.</p> <p>Toxicity.</p>	<p>133 patients were randomised to receive filgrastim (4 patients randomised to receive the factor were ineligible for evaluation) and 130 patients were randomised not to receive filgrastim.</p> <p><i>Efficacy</i> Significantly more patients in the filgrastim group (110 of 129 patients, 85%) received more than six cycles of chemotherapy compared with the non-filgrastim group (91 of 130 patients, 70%, $p = 0.03$).</p> <p>Relative dose-intensity achieved for etoposide, ifosfamide and cisplatin were significantly greater for the patients treated by filgrastim.</p> <p>Patients treated by filgrastim had significantly fewer delays for haematological reasons ($p < 0.001$).</p> <p>Grade 3 to 4 neutropenia was more frequent in the non-filgrastim arm ($p < 0.001$) but thrombocytopenia was more frequent among patients treated by filgrastim ($p < 0.001$).</p> <p><i>Toxicity</i> Neutropenic fever was less frequent in patients who were treated by filgrastim ($p = 0.52$).</p> <p>13 deaths owing to chemotherapy toxicity were seen. Ten of these were seen in the 130 patients in the non-filgrastim arm (8%; 95% CI: 4% to 14%) while only three were seen among the 129 patients treated with filgrastim (2%; 95% CI: 0% to 7%). No significance difference in failure-free or overall survival was seen.</p>	<p>This study was conducted as a sub-protocol to an assessment of BOB/VIP-B and BEB/EP.</p> <p>No p values were given for failure-free or overall survival.</p>	<p><i>Randomisation</i> The sub-protocol randomisation was based on a 2 x 2 factorial design. All comparisons of treatment were stratified for group (EORTC/MRC) and for the chemotherapy administered in line with the principle protocol randomisation (BOP/VIP-B compared with BEP/EP).</p> <p><i>Allocation concealment</i> The report did not state the level of allocation concealment. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> The Mantel-Haenszel test was used for comparison of event rates. The Wilcoxon rank sum test was used to analyse chemotherapy dose-intensities and Kaplan-Meier plots were calculated for failure-free survival.</p> <p>The analysis was adjusted for an imbalance of risk between groups.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Levi, 1988. ²⁸ Australia, New Zealand II	To compare maintenance therapy (vincristine) with no therapy in advanced germ cell tumours.	<p><i>Participants</i> 260 patients with advanced germ cell tumours with inoperable Stage II or III disease. Mean age 29 (range 15 to 65). None had prior chemotherapy.</p> <p><i>Intervention</i> All patients received induction chemotherapy of cisplatin, vinblastine and bleomycin. Those patients who achieved complete remission (CR) status were randomised to 6 months maintenance chemotherapy with vinblastine (10mg/m² every 4 weeks) or no further treatment.</p> <p><i>Design</i> RCT.</p>	Survival. Toxicity. Response.	<p>253 patients were assessable for induction chemotherapy. Median follow-up was in excess of 5 years.</p> <p><i>Efficacy</i> Complete response was achieved in 183 (72%). 88 of the patients who achieved complete response were randomised to maintenance therapy (43) or no maintenance (45). Relapse occurred in 25 patients (8 after 1 year, 2 after 2 years). 11 patients (26%) relapsed on maintenance therapy, 7 patients (16%) relapsed on no maintenance. The relapse rate was not significantly different between the arms $p = 0.08$. Overall 68% patients were alive and disease-free.</p> <p><i>Toxicity</i> Toxicities included myelosuppression (7 deaths from septicaemia). Bleomycin-related lung toxicity developed in 46% of patients (and lead to 8 deaths).</p>	No separate analysis was conducted for survival for maintenance arm compared with no maintenance.	<p><i>Randomisation</i> RCT.</p> <p><i>Allocation concealment</i> A random number system was used. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> The response data were compared using χ^2 analysis. The duration of responses and survival were compared by log-rank analyses and constructed with Kaplan-Meiers method. Cox regression was used to determine prognostic variables.</p>



Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Javadpour, 1982. ²⁶ USA II	To compare cytoreductive surgery and chemotherapy compared with chemotherapy alone.	<p><i>Participants</i> 39 patients with advanced Stage III NSGCT poor prognosis patients (retroperitoneal disease, liver and lung metastases, vena cava obstruction) were entered.</p> <p><i>Intervention</i> Patients were randomised to cytoreductive surgery and chemotherapy (n = 19) or to receive chemotherapy alone (n = 20). Chemotherapy consisted of 2 regimes. Each regime was given in cycles of varying intensities. Regime 1 (n = 10) consisted of dactinomycin, vinblastine, cyclophosphamide and cisplatin (for cycles 1 to 24). For the intensive cycles, (cycles 1 and 8) bleomycin was added to the regime. Regime 2 (n = 29) consisted of the same drugs. All drugs were given in intensive cycles (1, 3 and 5) and in non-intensive cycles (2 and 4). For the remaining cycles (6 to 24), bleomycin was omitted for maintenance chemotherapy.</p> <p><i>Design</i> RCT.</p>	Complete and partial response.	<p>Follow-up was from 8 to 48 months (median 24 months). Patients were well-matched for histology and volume of disease. The most common surgical technique was the retroperitoneal approach.</p> <p><i>Efficacy</i> No significant difference in overall response rate for chemotherapy and surgery group (75%) and chemotherapy alone (84%). No significant difference was seen in the rates of complete responses among the patients treated with both chemotherapy and surgery (50%) and those treated with chemotherapy alone (37%). No significant difference was seen in the rates of partial responses among the patients treated with both chemotherapy and surgery (25%) and those treated with chemotherapy alone (47%). A trend towards improved survival among patients treated with chemotherapy alone was seen but this did not achieve a level of significance (p = 0.055). No results were given comparing the two regimes used to give chemotherapy.</p> <p><i>Toxicity</i> The principle side effect of surgery was oedema (32%). 2 deaths resulted from oedema. 100% of chemotherapy patients experienced alopecia, 97% experienced nausea and vomiting and mucositis was seen in 43% of chemotherapy patients. One death from bleomycin related toxicities was recorded.</p>	<p>The chemotherapy regime varied, confounding the analysis. Only a small number of patients were enrolled.</p>	<p><i>Randomisation</i> RCT.</p> <p><i>Allocation concealment</i> Randomisation was performed using randomisation decks (Biometric Research Branch NCI) to provide 2 treatment groups. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Survival was estimated by the Kaplan Meier method and compared with the Wilcox Test of Gehan. All estimates of the probability of error are two-sided.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Kaye, 1998. ⁴⁸ UK II	To assess the efficacy of an intensive induction-sequential chemotherapy schedule compared with a regimen based on bleomycin, etoposide and cisplatin (BEP) for the treatment of patients with poor prognosis metastatic NSGCTs.	<p><i>Participants</i> Patients with histologically proven poor prognosis metastatic NSGCTs who were less than 65 years of age (mean 30) and who had not had prior chemotherapy, radiotherapy.</p> <p><i>Intervention</i> Induction – Sequential chemotherapy with bleomycin, vincristine and cisplatin (BOP) alternating with etoposide, ifosfamide, cisplatin and bleomycin (VIP-B). Intensive compared with a regimen based on bleomycin, etoposide and cisplatin (BEP)/etoposide and cisplatin (EP).</p> <p>Overall survival, time to progression and duration of complete responses were also assessed.</p> <p><i>Design</i> Multicentre RCT.</p>	Response. Failure-free survival. Overall survival.	<p>Median follow-up of 3.1 years. 28% had progressive disease.</p> <p><i>Efficacy</i> 380 patients were randomised. 79% of patients received at least six cycles of chemotherapy. The median duration of treatment was 18 weeks for BEP/EP and 14 weeks for BOP/VIP-B.</p> <p>The rates of complete responses were 57% for patients treated with the BEP/EP regimen and 54% for the patients treated with the BOP/VIP-B regime (p = 0.687). Failure-free survival at 1 year was 60% for patients treated with the BEP/EP regime (95% CI: 53% to 67%) and 53% for patients treated with the BOP/VIP-B regime (95% CI: 46% to 61%); (HR 1.28, 95% CI: 0.95 to 1.72, p = 0.101).</p> <p>Overall survival was higher in the patients treated by the BEP/EP regime (HR 1.30, 95% CI: 0.88 to 1.92, p = 0.190). 101 patients died (27%).</p> <p><i>Toxicity</i> Myelosuppression, febrile neutropenia and weight loss greater with BOP/VIP-B. More deaths owing to toxicities were seen in patients who were treated with BOP/VIP-B – 18 deaths (9%) – than among those treated with BEP/EP – (9 deaths (5).</p>	Poor prognosis features were defined in accordance with MRC guidelines, 1985.	<p><i>Randomisation</i> Multicentre RCT.</p> <p><i>Allocation concealment</i> Randomisation was conducted centrally.</p> <p><i>Completeness of patient data</i> Yes.</p> <p><i>Appropriate analysis of results</i> All comparisons of the two treatment regimens were stratified by group and for filgrastim treatment. Toxicity assessed using the Mantel-Haenszel χ^2 statistic. Hazard ratios, P values with p values were calculated and the time-to-event curves estimated using the Kaplan Meier method.</p>
Nichols, 1991. ⁴⁵ USA II	To compare efficacy and toxicity of etoposide and bleomycin with either standard dose cisplatin or high-dose cisplatin.	<p><i>Participants</i> 159 patients with disseminated germ cell cancer of advanced stage. All primary sites, histology, age and performance status included. None had prior chemotherapy.</p> <p><i>Intervention</i> The standard dose regime consisted of etoposide (100mg/m² days 1 to 5), bleomycin (30U IV weekly for 12 weeks) and cisplatin (20mg/m² days</p>	Complete response. Disease-free survival. Overall survival. NED. Toxicities.	<p><i>Efficacy</i> 78 patients were randomised to the standard dose regime and of these, 77 patients were eligible for evaluation. 36 patients (46%) had a complete response and 20 patients (26%) became disease-free by resection. 81 patients were randomised to the high dose regime and of these, 76 patients were eligible for evaluation. 35 patients (45%) had a complete response and 17 patients (22%) became disease-free after surgery. Overall 73% and 68% became disease-free after standard and high dose respectively.</p>		<p><i>Randomisation</i> RCT.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Dose-intensity analysis was by the method of Hryniuk and Bush. Logistic regression was</p>





Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
		<p>1 to 5).</p> <p>The high dose regime was administered in the same manner but the with the dose of cisplatin doubled to 40mg/m².</p> <p>Each arms were scheduled to receive 4 cycles at 3 week intervals.</p> <p><i>Design</i> RCT.</p>		<p>8 and 3 relapsed on standard and high dose, respectively.</p> <p>Overall 61% of patients treated with the standard dose regime and 63% of patients treated with the high dose regime were alive (median follow-up 24 months). No significant difference was seen in overall survival (p = 0.977).</p> <p><i>Toxicity</i> Significantly more ototoxicity, neurotoxicity and gastrointestinal toxicity were seen in the high dose group with high dose (p < 0.001).</p>		<p>used for dose-intensity/response relationship.</p> <p>Fischer's exact test was used to compare response and toxicity. Survival was plotted by the Kaplan Meier method. Patients were evaluated after 4 courses for response. Complete response (CR) was defined as disappearance of all radiographic and serological evidence of disease, partial response (50% reduction) and survival.</p>
<p>Ozols, 1988.⁴² USA II</p>	<p>To compare high dose chemotherapy (PVBE) with standard dose chemotherapy (PVB).</p>	<p><i>Participants</i> 52 patients with poor prognosis NSGCTs.</p> <p>Patients had any of the following – advanced abdominal disease, obstructive uropathy, metastases in liver, lung or brain.</p> <p><i>Intervention</i> Patients were randomised to receive 3 cycles of PVBE (34 patients) or 4 cycles of PVB (18 patients).</p> <p>PVBE was given every 3 weeks and consisted of cisplatin (40mg/m² days 1 to 5), vinblastine (0.2mg/m² day 1), bleomycin (30U iv days 1,8, 15) and etoposide (100mg/m² days 1 to 5).</p> <p>PVB was given every 3 weeks and consisted of cisplatin (20mg/m² days 1 to 5), vinblastine (0.3mg/m² day 1) and bleomycin (30U iv days 1,8, 15).</p> <p><i>Design</i> RCT.</p>	<p>Disease-free survival.</p> <p>Complete response.</p> <p>Relapse rates.</p> <p>Overall survival.</p> <p>Toxicity</p>	<p>Median follow-up 4 years.</p> <p><i>Efficacy</i> The complete response rate was 88% among patients treated with the high dose PVBE compared with 67% for patients treated with PVB (p = 0.14).</p> <p>The relapse rate for patients treated with PVBE was 17% compared with 41% for patients treated with the PVB regimen (p = 0.2).</p> <p>Median survival for patients treated with the PVBE regimen was greater than 48 months and was 30 months for patients treated with the PVB regimen.</p> <p>5 year survival rates were 78% for patients treated with the PVBE and 48% for patients treated in accordance with the PVB protocol (p = 0.06).</p> <p>Disease-free survival was higher among patients who were treated using the PVBE than among the patients treated using the PVB regime (p = 0.03).</p> <p>Disease-free survival was higher among patients treated using the PVBE regime (23 of 34, 68%) as compared with those patients treated with PVB (6 of 18, 33%) (p = 0.02).</p> <p><i>Toxicity</i> Myelosuppression was seen in 91% of patients treated</p>		<p><i>Randomisation</i> RCT. Stratification was by CNS involvement and primary sites.</p> <p>Randomisation was 2 to 1 in favour of PV.</p> <p><i>Allocation concealment</i> Randomisation was performed by the biostatistics and data management section of the clinical oncology program.</p> <p>The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> The Kaplan-Meier method was used for survival analysis and compared by the Mantel-Cox test.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
				<p>by the PVBE regime and in 50% of patients treated by the PVB regime ($p = 0.05$).</p> <p>Ototoxicity was diagnosed in 12 patients given the PVBE regime and 2 patients treated by the PVB regime.</p> <p>Each regime led to a pulmonary fibrosis rate of 6%.</p>		
Williams, 1987. ²² USA II	To compare the efficacy and toxicity of BEP with PVB in patients with disseminated germ cell tumours.	<p><i>Participants</i> 244 patients with disseminated germ cell tumours.</p> <p>Patients were eligible regardless of age, performance status or metastatic site.</p> <p><i>Intervention</i> Patients were randomised to receive either BEP ($n = 123$) or PVB ($n = 121$).</p> <p>BEP consisted of bleomycin IV 30U days 2, 9 and 16, etoposide 100mg/m² days 1 to 5, cisplatin 20mg/m² days 1 to 5.</p> <p>PVB consisted of a similar regimen but with the substitution of etoposide (0.15mg/kg days 1 and 2) for vinblastine.</p> <p><i>Design</i> Multicentre randomised prospective trial.</p>	<p>Complete response.</p> <p>Relapse rate.</p> <p>Survival.</p> <p>Toxicity.</p>	<p>Median follow-up was 90 weeks.</p> <p><i>Efficacy</i> 74 patients on PVB (61%) had a complete response, an additional 15 became disease-free after resection. 74 patients on BEP (61%) had a complete response, an additional 28 became disease-free after resection.</p> <p>74% of patients who were treated with PVB and 83% of patients who were treated with BEP responded.</p> <p>15 patients (16%) had recurrence. Of these 9 patients were treated with PVB and 6 of the patients were treated with BEP.</p> <p>The 2 year survival was approximately 80% in both treatment arms ($p = 0.11$).</p> <p><i>Toxicity</i> 59% of patients had granulocytopenia. Thrombocytopenia was more common in patients treated with the BEP regime ($p = 0.03$). Six patients had severe nephrotoxicity. Nausea and vomiting were common and of similar severity in both arms.</p> <p>Neurotoxicity was less severe with BEP – parathesias ($p = 0.02$), abdominal cramps ($p = 0.0008$) and myalgias ($p = 0.00002$).</p>	The dose of etoposide was lower than that used by Royal Marsden hospital investigators (120mg/m ² per day).	<p><i>Randomisation</i> Multicentre randomised prospective trial.</p> <p><i>Allocation concealment</i> Patients were randomly assigned by telephone. Balanced within each stratum in blocks of four. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Survival analysis was by Kaplan Meier method and compared with log rank analysis. Comparisons were made using χ^2 analysis.</p>



Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Wozniak, 1991. ³² USA II	To compare cisplatin, vinblastine and bleomycin with cisplatin, vinblastine and etoposide in advanced germ cell tumours.	<p><i>Participants</i> 160 assessable patients with disseminated testicular germ cell tumours were studied. 64 had minimal metastatic disease and 114 had maximal disease.</p> <p><i>Intervention</i> Patients were randomised to induction chemotherapy with PVB or PVE.</p> <p>Four cycles were given with a 3 week interval.</p> <p>PVB consisted of cisplatin (120mg/m² day 3), vinblastine (12mg/m² day 1) and bleomycin (15U/m² twice per week).</p> <p>PVE consisted of vinblastine (8mg/m² day 1), cisplatin (120mg/m² day 3) and etoposide (50mg/m² days 2 and 5).</p> <p>Cytoreductive surgery was done if complete response (CR) was not achieved.</p> <p><i>Design</i> RCT.</p>	<p>Complete response to chemotherapy.</p> <p>Disease-free survival.</p> <p>Relapse.</p> <p>Toxicity.</p> <p>Overall survival.</p>	<p>77 patients were randomised to PVB and 83 to PVE. Median follow-up 3.4 years.</p> <p><i>Efficacy</i> 77% of patients who were treated with PVB and 73% of patients who were treated with PVE achieved disease-free status (p = 0.39).</p> <p>5 patients who were treated with PVB and 4 patients who were treated with PVE relapsed. (7 of these 8 patients recurred with maximal disease.)</p> <p>No difference in survival (p = 0.19)</p> <p><i>Toxicity</i> Leukocyte nadirs were similar in both arms.</p> <p>The platelet nadir was lower in patients who were treated with VPE (p = 0.03).</p> <p>Neurotoxicity was higher in the cases of patients treated with PVB (p = 0.006).</p>		<p><i>Randomisation</i> Randomisation was carried out remotely at the SWOG Biostatistic Office. Patients were stratified by performance status, histology and extent of disease. The trial was designed to have an 80% chance of detecting a difference in the rate of complete response from 62% in PVB arm to 82% in PVE arm.</p> <p><i>Allocation concealment</i> Registration and randomisation was conducted at a central trials office.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Survival curves plotted by Kaplan-Meier method. Other comparisons by adjusted χ^2.</p>

Table 6.7: Metastatic seminoma: chemotherapy

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Oliver, 2000. ⁵⁴ UK I	To compare chemotherapy regimens with and without bleomycin in the first-line treatment of testicular or extra-gonadal germ cell tumours.	<p><i>Participants</i> Men with confirmed germ cell tumours undergoing first line therapy.</p> <p><i>Interventions</i> Combination chemotherapy regimens with and without bleomycin.</p> <p><i>Design</i> RCTs (2 arms).</p>	<p>Complete response.</p> <p>Relapse rate.</p> <p>Disease-free survival.</p> <p>Overall survival.</p> <p>Toxicity.</p>	<p>7 RCTs, with a total of 1,549 patients. Of these 1,478 patients were suitable for evaluation.</p> <p>Four trials included patients with good prognosis germ cell tumours. The remaining three trials included patients with advanced disease and poor prognosis.</p> <p>A higher percentage of patients in the bleomycin containing arms had complete remission, better disease-free survival and increased overall survival.</p> <p>The proportion of patients who were classified as complete responders was significantly improved with bleomycin in one trial (92% compared with 85%, $p = 0.028$), after chemotherapy alone and after debulking surgery (95% compared with 87%, $p = 0.016$).</p> <p>2 trials showed a statistically significant difference in disease-free survival and overall survival between the bleomycin and non-bleomycin arms.</p> <p>Analysis of groups of trials with similar chemotherapy combinations using the (χ^2 test) saw significant improvements in disease-free survival ($p = 0.00098$) and overall survival ($p = 0.00986$).</p> <p><i>Toxicity</i> 5 out of 7 trials reported higher lung toxicity in bleomycin containing regimens.</p> <p>The haematological toxicity of regimens containing bleomycin was significantly higher than other regimes but remained lower than that of the VIP regimen.</p>	<p>Unpublished analysis.</p> <p>Completed review will provide more methodological information and results.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE, Cancerlit, EMBASE, Cochrane data base, ASOC and ECCO.</p> <p><i>Inclusion criteria</i> Not stated.</p> <p><i>Quality assessment</i> Not stated</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> The χ^2 test was used to determine difference in disease-free and overall survival.</p>





Table 6.8: Metastatic seminoma: chemotherapy

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Clemm, 2000. ⁵⁶ Germany II	To compare single agent carboplatin with combined cisplatin, etoposide and ifosfamide in advanced metastatic seminoma.	<p><i>Participants</i> 251 evaluable patients with advanced metastatic seminoma.</p> <p><i>Intervention</i> Patients were randomised to receive either Arm A or Arm B. Arm A consisted of cisplatin (20mg/m²), etoposide (75mg/m²) and ifosfamide (1,2 g/m² days 1 to 5). Arm B consisted of carboplatin monotherapy (400mg/m²) every 4 weeks.</p> <p><i>Design</i> RCT.</p>	Response rates. Relapse rates. Toxicity. Overall survival.	<p><i>Efficacy</i> Following 4 to 6 cycles of chemotherapy, 234 patients (93%) had reached complete or partial response. 3 patients had no change, 3 patients had marker elevation and 7 patients had progressive disease. 30 patients (12%) relapsed after 3 to 60 months. Of these, 5 patients had been randomised to Arm A and 25 patients had been randomised to Arm B. At a median follow-up 52 months, overall survival was 92% with no significant difference between Arm A (95%) and Arm B (87%).</p> <p><i>Toxicity</i> Grade 3 to 4 thrombocytopenia was seen in 67 of 93 evaluable patients (72%) who had been randomised to Arm A as compared with 7 of 89 patients (8%) who had been randomised to Arm B.</p>	This study was published in abstract form only.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> The report did not give such information as to judge the level of allocation concealment. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> No information was given on the methods of analysis employed.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
DeWys, 1979. ⁴⁴ USA II	<p>To compare low and high dose cisplatin, in combination with other cytotoxics, for response inpatients with advanced germ cell cancer.</p> <p>To further compare either a 3 drug program with a cyclic crossover chemotherapy.</p>	<p><i>Participants</i> 45 patients with Stage III germ cell tumours.</p> <p><i>Interventions</i> Patients were randomised to receive cyclophosphamide (600mg/m² day 1), dactinomycin (1.0mg/m² day 1), vinblastine (4mg/m² day 1) and cisplatin (20mg/1 hour) with mannitol dieresis or to receive the same combination of drugs but with the dose of cisplatin adjusted to 40mg/8 hours on days 1 and 8 with no mannitol.</p> <p>Patients with complete or partial response were then randomised to vinblastine, dactinomycin and cisplatin (40mg/m²) or to receive AVP (dactinomycin, vincristine and cisplatin), CAP (cyclophosphamide, dactinomycin and cisplatin) patient VAP (vinblastin, dactinomycin and cisplatin) at 3 week intervals and repeated every 9 weeks.</p> <p><i>Design</i> RCT.</p> <p>Patients were stratified by performance status and histology.</p> <p>Complete response was defined as the complete disappearance of clinically detectable disease and normalising of markers.</p>	<p>Response.</p> <p>Toxicity.</p>	<p><i>Efficacy</i> The overall rate of complete responses was 36% and the overall rate of partial responses was 47%. This was highest among patients with positive markers, supra-clavicular nodes and minimal pulmonary and abdominal disease.</p> <p><i>Toxicity</i> No difference in haematological or renal toxicities were noted.</p> <p><i>Sub-protocol results</i> Minimal data were presented on the sub-protocol. There were no significant differences in response rates to the two induction regimes.</p> <p>Longer follow-up was required to allow adequate analyses of the data.</p>	<p>Not much data was presented as preliminary results only were available.</p> <p>Attempts to find an update have failed.</p> <p>Coding of results makes interpretation difficult.</p>	<p><i>Randomised</i> RCT.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>



Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Horwich, 2000. ⁵⁵ UK II	To compare single agent carboplatin with etoposide and cisplatin in advanced metastatic seminoma.	<p><i>Participants</i> 130 patients with confirmed advanced testicular or extra-gonadal seminoma. Patients had no prior chemotherapy.</p> <p><i>Intervention</i> Patients were randomised to receive carboplatin (400mg/m² corrected for glomerular filtration rate outside the range 81 to 120ml/min on days 1 of a 21 day cycle for a total of 4 courses) or to receive etoposide (120mg/m² on days 1, 2 and 3) and cisplatin (20mg/m² days 1, 2, 3, 4 and 5 of each cycle).</p> <p><i>Design</i> RCT.</p>	<p>The primary end-point was progression-free survival at 3 years.</p> <p>Secondary endpoints included failure-free survival and toxicity.</p>	<p>Median follow-up 4.5 years. 81% of patients attended follow-up for at least 3 years.</p> <p><i>Efficacy</i> The estimated progression-free survival at 3 years was 71% with carboplatin (95% CI: 60% to 82%) and 81% for cisplatin/etoposide (95% CI: 71% to 90%), (HR (carboplatin against etoposide and bleomycin): 0.64, 95% CI: 0.32 to 1.28; log rank χ^2 1.52, p = 0.21).</p> <p>The 3 year survival rate 84% (95% CI: 75% to 92%) for carboplatin and 89% (95% CI: 81% to 96%) with cisplatin/etoposide, (HR 0.85, (95% CI: 0.35 to 2.10; log rank χ^2 0.12, p = 0.73).</p>	<p>This trial was closed prematurely by the data monitoring committee.</p>	<p><i>Randomisation</i> Patients were randomised by telephone. Treatment was allocated in blocks to allow for centre and stage. The study was designed as an equivalence study to exclude a reduction in progression-free survival (PFS) with carboplatin of between 10% and 15% requiring 250 patients (90% power to achieve a 5% level of significance).</p> <p><i>Allocation concealment</i> Telephone to MRC. The report did not state if the study was blinded.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Test statistics were calculated using the Kaplan-Meier method and compared with the log-rank test. The Cox proportional hazards regression test was used to calculate the hazard ratio.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Nichols, 1991. ⁴⁵ USA II	To compare the efficacy and toxicity of etoposide and bleomycin with either standard dose cisplatin or high-dose cisplatin.	<p><i>Participants</i> 159 patients with disseminated germ cell cancer of advanced stage. Patients of all primary sites, histologies, ages and performance statuses were included. None had prior chemotherapy.</p> <p><i>Interventions</i> All patients received etoposide (100mg/m² days 1 to 5) and bleomycin (30U IV weekly x 12). Patients were randomised to receive either a high dose of cisplatin (40mg/m² days 1 to 5.) or a standard dose of the drug (20mg/m² days 1 to 5). Each arm was cycled at 3 weekly intervals and patients were prescribed 4 cycles.</p> <p><i>Design</i> RCT.</p>	<p>Complete response was defined as the disappearance of all radiographic and serological evidence of disease.</p> <p>Partial response was defined as a minimum 50% reduction in radiographic and serological signs of disease.</p> <p>Survival.</p>	<p><i>Efficacy</i> 78 patients were randomised to the standard dose regime (n = 77 evaluable) – 36 patients (46%) had a complete response and 20 patients (26%) became disease-free by resection. 81 patients were randomised to receive the higher dose of cisplatin (n = 76 eligible). 35 patients (45%) had a complete response and 17 patients (22%) became disease-free after surgery. Overall 73% of patients who had received the lower dose and 68% of patients who had received the higher dose became disease-free following chemotherapy and (where indicated) surgery. 8 patients who had been treated with the lower dose of cisplatin and 3 patients who had been treated with the higher dose relapsed. 61% of patients who had been treated with the lower dose of cisplatin and 63% of patients who had been treated with the higher dose were alive at a median follow-up of 24 months. No significant difference in overall survival was noted (p = 0.9).</p> <p><i>Toxicity</i> Significantly more toxicity was seen among the patients treated by the higher dose of cisplatin (p < 0.001) and included increased ototoxicity, neurotoxicity and gastrointestinal effects.</p>	Dose escalation with cisplatin results in excessive toxicity without any accompanying therapeutic benefit.	<p><i>Randomised</i> RCT.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes. Dose-intensity analysis was conducted using the method of Hryniuk and Bush. Logistic regression was used for dose-intensity/response relationship. Fischer's exact test was used to compare response and toxicity. Survival was plotted by the Kaplan Meier method.</p>





Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Samson, 1984. ⁵⁷ USA II	To determine if high dose cisplatin, vincristine and bleomycin gives better response and survival compared with low dose cisplatin in advanced testicular cancer.	<p><i>Participants</i> 114 patients with germ cell tumours of testicular origin. Pure seminomas were included only if extra-nodal disease was present or if radiotherapy had failed.</p> <p><i>Intervention</i> All patients were given vincristine (12mg/m² day 1 and 29) and bleomycin (15U/m²). Cisplatin was administered in one of two doses, to which patients were randomly allocated. Patients randomised to receive high dose cisplatin received 120mg/m² monthly while those who were randomised to receive low dose cisplatin were administered 15mg/m² daily for 5 days. Both the high and low dose regimes were cycled monthly for 4 months.</p> <p>Patients in complete remission received maintenance chemotherapy consisting of cyclophosphamide, 750mg/m² day 1; dactinomycin 1.2mg/m² day 1, doxorubicin 60mg/m² day 29 and vinblastine 12mg/m² day 58.</p> <p>Patients in partial remission underwent cytoreductive surgery. Those who subsequently achieved disease-free status also received maintenance chemotherapy.</p> <p><i>Design</i> RCT.</p> <p>Prior to randomisation patients were stratified by performance status and histology.</p>	Response. Toxicity. Survival.	<p>56 patients received the high dose regime and 58 patients were administered the low dose therapy.</p> <p>The minimum follow-up time of 55 weeks.</p> <p><i>Efficacy</i> 60 patients (53%) achieved a complete response and 42 patients (37%) achieved a partial response giving an overall response rate of 89%.</p> <p>Additionally 11 patients (10%) achieved disease-free status following surgery.</p> <p>The overall response rate has higher among the patients treated with the higher dose of cisplatin (63%) than among the patients treated with the lower dose (63%) and this achieved statistical significance ($p = 0.03$).</p> <p>A survival advantage for high dose cisplatin was demonstrated ($p = 0.009$). Sub-analysis showed a survival advantage for patients with maximal disease ($p = 0.01$). This advantage was not seen in patients with a minimal burden of disease.</p> <p>4 patients relapsed I first year.</p> <p><i>Toxicity</i> Greater toxicity was seen among those patients who were treated with high dose therapy; leucopenia, renal neuromuscular effects and mucosal effects. These effects were however judged to be reversible.</p>	A less than two-fold increase in the dose of cisplatin resulted in higher complete response rate as well as a survival advantage.	<p><i>Randomised</i> RCT.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes. Survival curves were plotted by the Kaplan-Meier method and were compared by the Wilcoxon technique of Gehan. Response rates were compared by one-sided χ^2 test.</p>

Table 6.9: Sexual functioning following treatment for testicular cancer: systematic review

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods																																																								
Jonker-Pool, 2001. ⁵⁸ The Netherlands III	To determine sexual functioning, after treatment for testicular cancer.	<p><i>Participants</i> Patients who have undergone treatment for testicular cancer.</p> <p><i>Interventions</i> Surveillance. Radiotherapy. Chemotherapy. Surgery. Retroperitoneal lymph node dissection (RPLD).</p> <p><i>Design</i> Prospective and retrospective studies.</p>	<p>Loss of libido.</p> <p>Male erectile dysfunction.</p> <p>Ejaculation disorder.</p> <p>Decrease in sexual activity.</p> <p>Sexual dissatisfaction.</p>	<p>The review located 29 retrospective studies and 7 prospective studies (n = 2,775).</p> <p><i>Overall weighted mean sexual dysfunction incidence</i></p> <table border="0"> <tr><td>Loss of desire</td><td>20</td></tr> <tr><td>Male erectile disorder</td><td>11.5</td></tr> <tr><td>Orgasmic dysfunction</td><td>20</td></tr> <tr><td>Ejaculation disorder</td><td>44</td></tr> <tr><td>Decrease in sexual activity</td><td>24</td></tr> <tr><td>Sexual dissatisfaction</td><td>19</td></tr> <tr><td>Mean response rate</td><td>77</td></tr> </table> <p><i>Surveillance</i></p> <table border="0"> <tr><td>Loss of desire</td><td>25</td></tr> <tr><td>Erectile disorder</td><td>7</td></tr> <tr><td>Orgasmic dysfunction</td><td>24</td></tr> <tr><td>Ejaculation disorder</td><td>16</td></tr> <tr><td>Decreased sexual activity</td><td>11</td></tr> <tr><td>Sexual dissatisfaction</td><td>8</td></tr> </table> <p><i>Radiotherapy</i></p> <table border="0"> <tr><td>Loss of desire</td><td>14</td></tr> <tr><td>Male erectile disorder</td><td>25</td></tr> <tr><td>Orgasmic dysfunction</td><td>23</td></tr> <tr><td>Ejaculation disorder</td><td>40</td></tr> <tr><td>Decrease in sexual activity</td><td>29</td></tr> <tr><td>Sexual dissatisfaction</td><td>16</td></tr> </table> <p><i>Chemotherapy</i></p> <table border="0"> <tr><td>Loss of desire</td><td>25</td></tr> <tr><td>Male erectile disorder</td><td>11</td></tr> <tr><td>Orgasmic dysfunction</td><td>28</td></tr> <tr><td>Ejaculation disorder</td><td>28</td></tr> <tr><td>Decreased sexual activity</td><td>34</td></tr> <tr><td>Sexual dissatisfaction</td><td>15</td></tr> </table> <p><i>Chemotherapy (PCT) with surgery</i></p> <table border="0"> <tr><td>Loss of desire</td><td>13</td></tr> <tr><td>Male erectile disorder</td><td>11</td></tr> <tr><td>Orgasmic dysfunction</td><td>22</td></tr> </table>	Loss of desire	20	Male erectile disorder	11.5	Orgasmic dysfunction	20	Ejaculation disorder	44	Decrease in sexual activity	24	Sexual dissatisfaction	19	Mean response rate	77	Loss of desire	25	Erectile disorder	7	Orgasmic dysfunction	24	Ejaculation disorder	16	Decreased sexual activity	11	Sexual dissatisfaction	8	Loss of desire	14	Male erectile disorder	25	Orgasmic dysfunction	23	Ejaculation disorder	40	Decrease in sexual activity	29	Sexual dissatisfaction	16	Loss of desire	25	Male erectile disorder	11	Orgasmic dysfunction	28	Ejaculation disorder	28	Decreased sexual activity	34	Sexual dissatisfaction	15	Loss of desire	13	Male erectile disorder	11	Orgasmic dysfunction	22	Statistical methodology is unclear.	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE and PsycLIT were searched from 1975 to 2000.</p> <p><i>Inclusion criteria</i> Studies were inclusion of the majority of sexual dysfunction parameters used as criteria.</p> <p><i>Quality assessment</i> Not stated</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Heterogeneity of studies determined.</p> <p>Trends were identified using outcomes of dependent variables.</p>
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Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
				<p>Ejaculation disorder 62 Decreased sexual activity 29 Sexual dissatisfaction 20</p> <p><i>Retroperitoneal lymph node dissection</i> Loss of desire 66 Male erectile disorder 10 Orgasmic dysfunction 11 Ejaculation disorder 81 Decreased sexual activity 0</p> <p><i>Combined PCT Chemotherapy, retroperitoneal lymph node dissection and radiotherapy</i> Loss of desire not reported Male erectile disorder 24 Orgasmic dysfunction 55 Ejaculation disorder 60 Decrease in sexual activity not reported Sexual dissatisfaction not reported.</p> <p>All treatment modalities reported a decrease in sexual desire, orgasmic intensity, sexual activity and sexual satisfaction. There was no apparent reduction in sexual dysfunction in patients treated by medically less invasive treatments.</p>		

Table 6.10: Chemotherapy after radiotherapy for metastatic seminoma: primary studies.

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Duchesne, 1997. ⁶¹ UK VI	To evaluate the efficacy of chemotherapy after radiotherapy for metastatic seminoma.	<p><i>Participants</i> Patients with metastatic testicular seminoma treated with chemotherapy between 1978 and 1990 in 9 UK centres and 1 Norwegian centre.</p> <p><i>Interventions</i> Chemotherapy as primary treatment; the majority received platinum-based therapy. Approximately half of the patients received adjuvant radiotherapy.</p> <p><i>Design</i> Retrospective study.</p>	Progression-free survival.	<p>302 patients were included. Patients had normal AFP levels. All patients had undergone an orchidectomy. The median follow-up 6.5 years.</p> <p><i>Efficacy</i> 54 patients had disease progression and 48 patients have died. 128 patients entered complete remission with chemotherapy alone (42%).</p> <p>174 patients had residual disease on completion of chemotherapy.</p> <p>Prognostic factors for progression included visceral metastases, raised pre-chemotherapy LDH levels, residual post-chemotherapy disease at visceral sites.</p> <p>In patients receiving platinum-based chemotherapy, there was no significant difference in progression-free survival whether radiotherapy was used or not.</p> <p>Patients receiving BEP had a progression-free survival rate of 88% (95% CI: 80 to 96). This was uninfluenced by post-chemotherapy radiotherapy.</p> <p>The absolute benefit to patients with residual masses confined to the abdomen was estimated to be 2.3%.</p>	Data from 10 centres were used. Therefore patient selection may have affected results.	<p><i>Randomisation</i> No.</p> <p><i>Allocation concealment</i> Not applicable.</p> <p><i>Completeness of patient data</i> Yes.</p> <p><i>Appropriate analysis of results</i> The Kaplan-Meier method of analysis was used to assess the progression-free survival rates and were compared with the log-rank test. Post-chemotherapy radiotherapy was assessed using Cox's proportional hazards regression model.</p>



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Penile Cancer

The Questions

- a) How effective is penis-conserving therapy as a curative option?
- b) How effective is prophylactic lymph node dissection?
- c) How effective is therapeutic lymph node dissection for patients with proven lymph node metastases?
- d) How effective is chemotherapy for metastatic disease?

The Nature of the Research Evidence

a) **Penis conserving therapy**

No randomised trials addressing any treatment issue in penile cancer have been found. The evidence is based entirely on observational and usually retrospective studies. It is predominantly low quality evidence as a result. Even in the largest series, there is considerable heterogeneity within the patient population and in many instances considerable heterogeneity in the treatment protocols. This compounds the difficulties in drawing conclusions from these retrospective reports.

Four retrospective studies evaluating total or partial penile amputation were identified.¹⁻⁴ The total number of patients in these four studies was 559. Three retrospective studies described outcomes with external beam radiotherapy,⁵⁻⁷ two with interstitial radiotherapy,^{6, 8} one with circumcision,⁹ one with laser therapy,¹⁰ and one with combined chemotherapy and radiotherapy.¹¹ One study reported outcomes of Iridium-192 brachytherapy.¹² Quality of life following partial penectomy was reported in one small study.¹³

b) **Prophylactic lymph node dissection**

Ten retrospective studies described the results of surveillance or prophylactic lymph node dissection.^{2, 4, 9, 14-20} The effectiveness of sentinel lymph node dissection was reported in one study.²¹

c) **Therapeutic lymph node dissection**

Four studies described outcomes of therapeutic lymph node dissection.^{16, 22-24}

d) **Chemotherapy**

Long-term survival data for penile carcinoma were presented in one retrospective study.⁹ The effectiveness and toxicity of combination chemotherapy for the treatment of locally advanced or metastatic penile carcinoma was described in one phase II trial.²⁵

Summary of the Research Evidence

a) Penis conserving therapy

Total or partial penile amputation is the most common treatment for penile cancer.¹⁻⁴ Partial penectomy might be possible in some patients;³ selected patients might be cured with surgical margins of less than 1cm. Reports from units undertaking penis conserving therapy indicate, however, that cure is also possible in selected patients without resorting to partial or total amputation. No direct comparison of the efficacy of penis-conserving therapy in contrast to partial or complete amputation can be made, though non-randomised reports have suggested the possibility of higher local failure rates with conservative therapy, which, with appropriate salvage therapy, yield ultimate survival rates that are similar. Alternatives to penile amputation include external beam radiotherapy, interstitial radiotherapy, circumcision alone (in suitable patients) and laser therapy.⁴⁻¹² It is also possible that combined chemo-radiotherapy merits further study.¹¹ Few studies have examined the quality of life implications of penile amputation. A study of 14 patients who had undergone partial penectomy, suggested that quality of life, in terms of social, psychological and sexual relationships, can be maintained in the majority of patients.¹³

Conclusion

Options for primary treatment of penile cancer include conservative surgery, external beam radiotherapy, brachytherapy, chemotherapy-radiotherapy and laser therapy.

b) Prophylactic lymph node dissection

No RCTs of prophylactic lymph node dissection were identified. Several descriptive retrospective studies have indicated successful outcomes for some men managed either with this strategy or by surveillance and therapeutic lymph node dissection in cases of relapse.^{2, 4, 9, 14-20} Techniques such as sentinel node biopsy are associated with a proportion of false-negatives.²¹

Conclusion

It is unknown whether prophylactic lymph node dissection/radiotherapy are better than surveillance and salvage lymph node dissection/radiotherapy.

c) Therapeutic lymph node dissection

As with penis-conserving therapy, there is evidence from non-randomised reports that some patients with clinically or pathologically involved inguinal lymph nodes can be cured by therapeutic lymph node dissection but evidence is severely limited.^{16, 22, 23} Not all patients with palpable lymphadenopathy, however, are found to have lymph node metastases.^{22, 24}

Conclusion

No statements can be made regarding technique or the extent of surgery.

d) Chemotherapy

Patients with metastatic disease have a poor prognosis.⁹ There is evidence from a non-randomised study that patients with advanced, metastatic penile cancer

(involving iliac nodes or distant metastases) may respond to chemotherapy, including agents such as cisplatin, bleomycin and methotrexate. No statements can be made regarding the optimum regime or schedule or regarding the combination of chemotherapy with radiotherapy for primary disease.²⁵

Conclusion

The role of chemotherapy in metastatic penile cancer is not clear.

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Bladder Cancer

The Questions

- a) How effective are intravesical therapies following transurethral resection for superficial (Ta to T1, N0, M0) disease?
- b) How effective are surgery and radiotherapy for muscle-invasive (T2 to 4, N0, M0) disease?
- c) How effective are adjuvant or neo-adjuvant chemotherapy in muscle-invasive (T2 to 4, N0, M0) disease?
- d) How effective are systemic therapies in metastatic (lymph node or visceral) disease?

The Nature of the Research Evidence

a) Intravesical therapies

Six meta-analyses have evaluated the benefit of intravesical chemotherapy compared with transurethral resection alone in patients with superficial bladder cancer¹⁻⁷ (Table 8.1.a). A large meta-analysis of 11 RCTs confined to newly diagnosed patients reported recurrence rates following intravesical chemotherapy.¹ An analysis of five Japanese randomised trials has been reported.² An individual patient data meta-analysis of six randomised studies assessed adjuvant intravesical chemotherapy on tumour recurrence, disease progression and survival.^{3,4} Tumour recurrence and disease progression following intravesical chemotherapy and immunotherapy compared with TUR were reported in two meta-analyses of published data.^{5,6} Intravesical mitomycin was compared with intravesical Bacillus Calmette-Guerin (BCG) in a meta-analysis of six RCTs.⁷ Two systematic reviews report on the complications of intravesical BCG.^{8,9}

Three randomised trials were located¹⁰⁻¹² (Table 8.1b). One evaluated a single instillation of epirubicin;¹⁰ one evaluated a single instillation of mitomycin immediately following TUR¹¹ and the third study compared bladder irrigation with no irrigation following TUR.¹²

b) Surgery and radiotherapy

Two reviews were located^{13,14} (Table 8.2a). A Cochrane review included three randomised trials¹³ and compared radical radiotherapy with salvage cystectomy with pre-operative radiotherapy followed by radical cystectomy. One meta-analysis compared pre-operative radiation and cystectomy with cystectomy alone.¹⁴ There are no meta-analyses comparing radical radiotherapy with radical surgery in patients with muscle-invasive bladder cancer.

Six primary studies were located¹⁵⁻²⁰ (Table 8.2b). The efficacy and morbidity of radical external beam radiotherapy for muscle-invasive bladder cancer was

reported in two retrospective studies.^{15, 16} The long-term effects of radical cystectomy were reported in a study of 1,056 patients.¹⁷ One RCT has compared hyperfractionated high dose radiotherapy with conventional radiotherapy.¹⁸ Another randomised trial compared two hypofractionated radiotherapy schedules for the palliation of local symptoms of invasive disease.¹⁹ Quality of life for patients receiving either radical radiotherapy with salvage cystectomy or pre-operative radiotherapy followed by radical cystectomy is reported as part of a randomised study.²⁰

c) Adjuvant or neo-adjuvant chemotherapy

Two systematic reviews were located^{21,22} (Table 8.3a). Neo-adjuvant chemotherapy was evaluated in an individual patient data meta-analysis.²¹ One systematic review reported on neo-adjuvant and adjuvant chemotherapy.²²

Four randomised studies were located²³⁻²⁶ (Table 8.3b). The efficacy of neo-adjuvant CMV chemotherapy was determined in an MRC/EORTC RCT.²³ The efficacy of neo-adjuvant M-VAC was assessed in a SWOG randomised study.²⁴ Two randomised trials evaluated the efficacy of concurrent chemotherapy in muscle-invasive disease.^{25, 26}

d) Systemic therapies

Seven randomised trials of chemotherapy regimes were reported²⁷⁻³³ and one randomised trial investigated the timing of chemotherapy in high-risk patients.³⁴ (Table 8.4) An uncontrolled study,³⁵ reports long-term survival following chemotherapy. A retrospective review evaluates the role of surgical resection in metastatic urothelial cancer.³⁶

Summary of the Research Evidence

a) Intravesical therapies

A meta-analysis of 11 RCTs comparing intravesical chemotherapy using mitomycin, thiotepa, epirubicin, peplomycin, neocarzinostatin and mitoxantrone with TUR alone, showed that intravesical therapy was associated with a 44% reduction in tumour recurrence at one year with an odds ratio of 0.56 (95% CI: 0.48 to 0.65; $p < 0.00001$).¹ Intravesical schedules of short-term duration, one year and two year, were associated with a significant reduction in tumour recurrence at two years of 32%, 31% and 75%, respectively, suggesting that longer schedules may be more beneficial.

Data from 1,732 patients from five RCTs were analysed. Patients were treated with either TUR alone or intravesical chemotherapy with doxorubicin or epirubicin.² Using multivariate analysis, they reported that intravesical treatment reduced the risk of recurrence by 52% to 62%.

A combined individual patient data (IPD) meta-analysis of four EORTC and two MRC trials evaluated the benefit of immediate adjuvant intravesical chemotherapy compared with TUR alone.^{3, 4} Adjuvant therapy significantly reduced the recurrence rate and prolonged the disease-free interval with an absolute benefit in the percentage of patients disease-free at eight years of 8%. Two randomised trials evaluated in this meta-analysis showed that a single instillation of epirubicin¹⁰ or mitomycin¹¹ immediately following transurethral

resection decreased recurrence rates by nearly half when compared with either the instillation of water or no further treatment. Adjuvant intravesical chemotherapy did not reduce disease progression or the time to appearance of distant metastases nor did it prolong survival.

A meta-analysis of six RCTs of medium and high-risk patients with superficial bladder cancer reported a significant benefit of intravesical BCG compared with TUR alone in reducing tumour recurrence.⁶ The overall log hazard ratio for tumour recurrence was -0.83 (variance 0.02) which translates into a 56% reduction in the hazard of recurrence. The optimal strain, dose and schedule of BCG remains to be determined. However, this agent may be associated with a range of complications from local reactions to potentially fatal systemic reactions, including late epididymo-orchitis.^{8,9}

In a meta-analysis utilising a Bayesian statistical approach, intravesical therapy with thiotepa, doxorubicin, BCG and mitomycin decreased the probability of tumour recurrence compared with TUR alone.⁵ The calculated number of patients, which need to be treated in order to prevent one recurrence, ranged from 3.3 for BCG to ten for doxorubicin. Intravesical mitomycin or BCG were the recommended agents. However in a separate meta-analysis,⁷ BCG has been reported to be superior to mitomycin in reducing tumour recurrence in high risk patients. There was no difference between these agents in terms of disease progression or survival.

A MRC RCT comparing post-operative bladder irrigation with glycine compared with no irrigation was evaluated in patients with newly diagnosed Ta or T1 bladder cancer.¹² It was reported that irrigation was easy to administer, had little or no toxicity and produced an absolute improvement in the two year recurrence-free rate of 6%. Irrigation with glycine did not significantly alter overall survival with an absolute improvement of 1% at two years (92% compared with 91%) and 2% at five years (76% compared with 74%). Nevertheless, these results are encouraging and suggest that the effect of intravesical chemotherapy might be mediated, at least in part, by preventing free tumour cells from re-implanting in the bladder.

Conclusion

Adjuvant intravesical therapy or bladder irrigation delays recurrence in patients with superficial bladder cancer. For patients at a high risk of recurrence, BCG may be superior to other agents. The relative merits of irrigation and chemotherapy/BCG have not been defined.

b) Surgery and radiotherapy

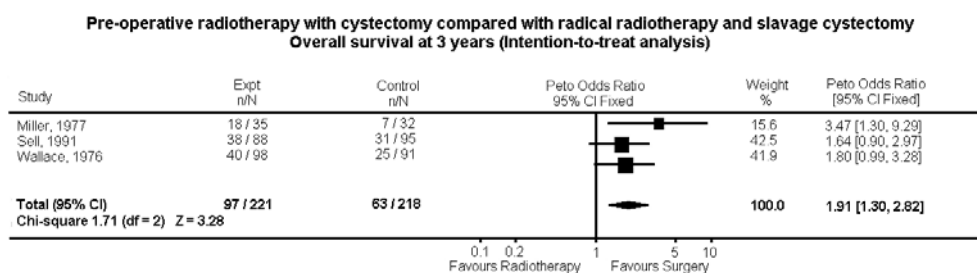
The comparison of modern radiotherapy with modern cystectomy is largely based on observational studies.

The efficacy and morbidity of radical external beam radiotherapy (40Gy to 60Gy, median 20 fractions) was evaluated in 120 patients in the UK with muscle-invasive bladder cancer.¹⁵ At 12 months, the overall morbidity was 12% (proctitis 8% and cystitis 4%). Tumour recurrence developed in 56% with an overall median survival of five years.

A population-based study from Ontario, Canada, reported the results of 1,372 patients treated with radical radiotherapy.¹⁶ Overall five year survival was 28% and cause-specific survival was 41%. A total of 25% of patients retained their bladders and the overall survival following salvage cystectomy was 28%. However, this report was taken from the records of patients treated between 1982 and 1994 and advances in radiotherapy since then might have impacted on current outcomes.¹⁶ Additionally, the patients in this study may have been selected, as the 1,372 cases treated with radiotherapy were a subset of the 20,906 patients diagnosed with bladder cancer in that time period.

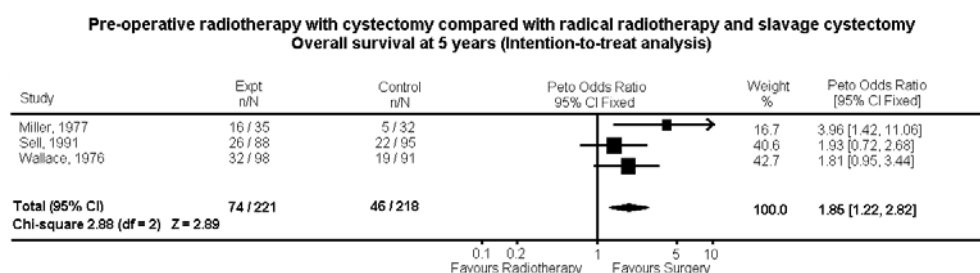
The long-term effects of radical cystectomy with pelvic lymph node dissection in 1,056 patients with invasive bladder cancer were reported.¹⁷ Perioperative death occurred in 3% of patients and early complications in 30%. Recurrence-free survival was 68% at five years and 60% at ten years. Overall survival at five and ten years were 66% and 43%, respectively. An improvement in the quality of life has been made with advancements in orthotopic urinary diversion.

Figure 8.1a:- Optimum combination of therapies – overall survival at three years:¹³



A meta-analysis compared pre-operative radiotherapy (40Gy to 50Gy in four to five weeks) and radical cystectomy compared with radical radiotherapy with salvage cystectomy.¹³ Three randomised trials were assessed which included 439 patients with Stage T2 to T4a disease. An intention-to-treat analysis for overall survival indicated a significant advantage to pre-operative radiotherapy and radical cystectomy at three years (odds ratio 1.91, 95% CI: 1.30 to 2.82; see Figure 8.1a) and at five years (odds ratio 1.85, 95% CI: 1.22 to 2.82 see Figure 8.1b). The mean overall survival at three and five years were 45% and 36% for pre-operative radiotherapy and radical cystectomy and 28% and 20% for radical radiotherapy with salvage cystectomy. However, because of advances in both radiotherapy and surgical techniques, it is questionable whether these results can be reliably extrapolated to modern practice.

Figure 8.1b:- Optimum combination of therapies – overall survival at five years:¹³



Quality of life was evaluated as part of an RCT comparing cystectomy with radical radiotherapy.²⁰ Patients were mailed a questionnaire at six months and 12 to 18 months post-treatment. At six months, the cystectomy group had more complaints of fatigue and required more home help owing to their urostomy than the radiotherapy group but otherwise the scores were similar. The major difference following the second questionnaire was that all cystectomised men had erectile impotence compared with 36% for the radiotherapy group.

The role of radiotherapy (20Gy to 54Gy) prior to cystectomy compared with cystectomy alone was evaluated in a meta-analysis of five RCTs.¹⁴ There was no significant difference in survival at three years with an odds ratio of 0.91 (95% CI: 0.64 to 1.30). Four trials included five year survival data and an intention-to-treat analysis indicated no significant benefit of pre-operative radiotherapy, compared with cystectomy alone for muscle-invasive bladder cancer (OR 0.71, 95% CI: 0.48 to 1.06). However, the trials included in this study were small and of poor quality.

168 patients with T2 to T4 carcinoma of the bladder were randomised to receive radiotherapy of either 1Gy three times a day to a total of 84Gy (hyperfractionated) or 2Gy once a day to a total of 64Gy (conventional).¹⁸ The results showed a significant survival benefit to the hyperfractionated group ($p < 0.01$). A randomised trial reported no difference in the palliation of local symptoms for invasive disease with 35Gy in ten fractions over two weeks compared with 21Gy in three fractions on alternate weekdays over one week.¹⁹

Conclusion

No randomised comparisons of modern radiotherapy compared with modern cystectomy for muscle-invasive bladder cancer have been made. It is possible that cystectomy provides increased local control at the expense of some morbidity but this is not confirmed by any RCTs.

c) Adjuvant or neo-adjuvant chemotherapy

The role of neo-adjuvant or adjuvant chemotherapy remains uncertain. The survival benefit of neo-adjuvant or concurrent platinum-based chemotherapy in patients with locally advanced bladder cancer was assessed in an individual patient data meta-analysis.^{21, 37} Data were obtained from four randomised trials, comprising 479 patients. Three trials completed chemotherapy before starting local therapy and one gave chemotherapy simultaneously with radiotherapy or radiotherapy and cystectomy. Individual patient data analysis suggests a small

non-significant benefit to local therapy alone with a hazard ratio of 1.02 (95% CI: 0.81 to 1.26, $p = 0.8$). Supplementation of these data with the published results of a fifth trial still showed no significant effect with chemotherapy ($p = 0.3$).

However, since the publication of this study, two further large studies have been performed. The MRC-EORTC study was published showing no survival benefit for neo-adjuvant CMV chemotherapy, prior to radiotherapy or cystectomy.²³ While more analysis has been performed, the results of this update are not available for comment and the findings are based on a relatively small number of events; as such no firm conclusions can yet be drawn. The SWOG trial of neo-adjuvant M-VAC chemotherapy showed a significant survival benefit for adjuvant chemotherapy, but this analysis was based on a one-sided test of significance.²⁴ The meta-analysis is currently being updated and more mature data from all studies are needed, but neo-adjuvant chemotherapy is a valid and legitimate area for continuing research. Trials of adjuvant chemotherapy, similarly, do not permit any definite conclusions about its role;²² this is the subject of an ongoing EORTC randomised trial.

The role of synchronous chemotherapy-radiotherapy has been evaluated in a randomised trial in which 99 patients with T2 to T4b tumours were selected for definitive radiotherapy or pre-cystectomy radiotherapy and randomised to cisplatin 100mg/m² at two week intervals for three cycles concurrent with radiotherapy or to no chemotherapy.²⁶ There was no difference in the rate of metastasis, but the pelvic relapse rate was significantly reduced in the cisplatin-treated patients ($p = 0.038$). There was no difference in overall survival. The RTOG 89-03 study randomised 123 men to concurrent chemo-radiotherapy with or without two cycles of prior MCV chemotherapy.²⁵ There were no significant differences in complete response rates or survival.

Conclusion

The roles of neo-adjuvant or adjuvant chemotherapy are still unclear. Further analysis of existing trials is awaited.

d) Systemic therapies

There is no doubt that transitional cell carcinoma of the bladder is a chemo-responsive disease, with response rates of around 46% to 65%.²⁹ However, no randomised trials have compared chemotherapy to best supportive care. The relief of symptoms (e.g. haematuria, lymphoedema) can only be presumed to be worthwhile in terms of quality of life. Several RCTs of chemotherapy regimes are available, however and have the following conclusions:

Cisplatin and methotrexate or cisplatin and cyclophosphamide are probably not superior to cisplatin alone in terms of response rate or survival. A randomised trial of 53 patients receiving either cisplatin alone or in combination with methotrexate, reported no difference in clinical response ($p = 0.18$) or survival ($p = 0.8$).²⁷ In another study of 109 patients randomised to either cisplatin alone or combined with cyclophosphamide, no significant difference in response was seen between the two arms.²⁸

M-VAC chemotherapy is superior to single agent cisplatin in terms of response rate and survival. In one randomised study 255 assessable patients were allocated to either cisplatin alone or in combination with methotrexate,

vinblastine and doxorubicin (M-VAC).²⁹ M-VAC significantly increased response rates, 65% compared with 46% ($p < 0.05$) and the median survival 48.3 weeks compared with 36.1 weeks ($p = 0.003$).

M-VAC appears to be superior to CisCA (cisplatin, cyclophosphamide, doxorubicin) in terms of response rates and survival. In a randomised study 110 patients with metastatic disease were randomised to receive either CisCA or M-VAC.³⁰ Overall response was significantly better for M-VAC (46% compared with 65%, $p < 0.05$) and median survival (48.35 weeks compared with 36.1 weeks).

No randomised trials have compared CMV chemotherapy with M-VAC.^{31, 38} CMV chemotherapy is superior to MV chemotherapy. In a Medical Research Council randomised trial, overall clinical response to CMV (108 patients) was 46% compared with 19% for MV (106 patients).³¹ Survival was significantly improved with CMV (HR 0.68, 95% CI 0.51 to 0.90, $p = 0.0065$).

The combination of Gemcitabine and Cisplatin (GC) appears to be equivalent to M-VAC in terms of response and survival, but is less toxic. In a trial of 405 patients randomised to either GC ($n = 203$) or M-VAC ($n = 202$), overall response rates were 54.3% for GC and 55% for M-VAC.³² The respective time to progressive disease was similar (HR 1.05, 95% CI 0.85 to 1.30, $p = 0.66$) as was overall survival (HR 1.04, 95% CI 0.82 to 1.32, $p = 0.75$). M-VAC resulted in more cases of grade 3 and 4 neutropenia, mucositis, infection and diarrhoea.

The timing of chemotherapy was investigated in a trial of 140 patients with high-risk urothelial cancer.³⁴ Patients were randomised to receive two courses of M-VAC before and three courses after cystectomy ($n = 70$) or five courses of M-VAC following cystectomy ($n = 70$). The combined M-VAC and surgery was active in this cohort with a median overall survival of 4.0 years. However, there was no significant difference in overall survival between the two arms ($p = 0.54$).

In a small randomised trial of 51 patients, the addition of paclitaxel to gemcitabine and cisplatin appeared to increase toxicity without improving response.³³ Occasional long-term survivors have been reported anecdotally following chemotherapy for metastatic urothelial cancer in an uncontrolled study,³⁵ but a retrospective review of such patients stresses the role of additional surgery and the very highly selected case-mix underlying such studies.³⁶

Conclusion

Combination chemotherapy has a role in the management of advanced or metastatic bladder cancer. The combination of cisplatin and gemcitabine is well tolerated and its efficacy appears to be comparable to the best reported regimes.

Table 8.1a: Superficial bladder cancer: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
EORTC /MRC, 1996. ^{3,4} Poland, Belgium, UK I	To evaluate the impact of prophylactic chemotherapy agents following primary resection on disease progression and survival in Ta and T1 bladder cancer.	<i>Participants</i> Patients with primary or recurrent Stage Ta and T1 transitional cell bladder cancer. <i>Interventions</i> Transurethral resection alone or with adjuvant prophylactic intravesical chemotherapy (thiotepa, VM-26, doxorubicin, epodyl, epirubicin, pyridoxine (oral) and mitomycin). <i>Design</i> All EORTC and MRC RCTs.	Time to first recurrence. Time to progression. Time to distant metastasis. Time to second primary tumour. Duration of survival (death from malignant disease). Progression-free survival.	4 EORTC and 2 MRC trials were included. An individual patient data analysis was conducted. Patient data were analysed on an intention-to-treat basis. Data from 2,535 patients were included. 906 patients had TUR alone and 1,629 patients received post-operative intravesical chemotherapy. <i>Efficacy</i> Adjuvant therapy significantly reduced recurrence rate and increased the disease-free interval ($p < 0.01$). After a median follow-up of 7.8 years, there was no advantage for adjuvant therapy in terms of disease progression, time to appearance of distant metastases or survival.	Patients who did not receive chemotherapy preceded to receive chemotherapy on recurrence; this has complicated the analysis of time to progression data and survival data analysis. No trials using BCG included. Combined trials using different drugs.	<i>Review question</i> Yes <i>Literature search</i> None. <i>Inclusion criteria</i> All EORTC and MRC prophylactic, RCTs in primary or recurrent TCC at Stage Ta/T1 bladder cancer assessing TUR with or without adjuvant treatment. <i>Quality assessment</i> Not given. <i>Study details</i> Not given. <i>Appropriate synthesis of results</i> Yes.
Hinotsu, 1999. ² Japan I	To determine the effect of intravesical chemotherapy (doxorubicin or epirubicin) after TUR on tumour recurrence and the absolute risk after TUR alone.	<i>Participants</i> Patients with Ta or T1 grades 1 to 2 superficial bladder cancer. <i>Interventions</i> Transurethral resection and intravesical chemotherapy. All patients underwent TUR. Patients were randomised to receive intravesical doxorubicin or epirubicin or no further treatment. <i>Design</i> Multivariate analysis of 5 RCTs.	Tumour recurrence	Data from 1, 732 patients contributed to this meta-analysis of 5 Japanese RCTs. Patients were stratified by recurrence status (primary against recurrent) and by the number of tumours (single against multiple). Intravesical treatment reduced the risk of recurrence by 56% (with a range of 52% to 62% on multivariate analysis). Two types of recurrence after TUR were identified by the smoothed hazard analysis – early and late. Hazard function analyses found in each subgroup a prophylaxis prevented recurrence during the 500 days after TUR but the beneficial effect was not seen after this time period. This suggests that prophylaxis delayed but did not prevent recurrence.	No criteria was given for selected studies. No search strategy was provided. Different inclusion criteria were used in the 5 trials which were combined. Patients in the surgery and chemotherapy treatment group received either doxorubicin or epirubicin but at different doses and schedules.	<i>Review question</i> Yes <i>Literature search</i> 5 RCTs were conducted under the auspices of the JUCRGA and were chosen for analysis. <i>Inclusion criteria</i> Tis and Tx were excluded as were patients with G0 or GX disease. <i>Quality assessment</i> Not given <i>Study details</i> Yes <i>Appropriate synthesis of results</i> Yes

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Huncharek, 2000. ¹ USA I	To quantify the effect of intravesical chemotherapy on tumour recurrence following complete transurethral resection in newly diagnosed superficial bladder cancer.	<p><i>Participants</i> 3,730 patients with Ta/T1 G1 to G3 bladder cancer.</p> <p><i>Interventions</i> Intravesical chemotherapy with doxorubicin, mitomycin, thiotepa, epirubin, peplomycin, neocarzinostat or mitoxantrone.</p> <p>The duration of treatment varied.</p> <p>from a single instillation to a two-year schedule.</p> <p><i>Design</i> Published RCTs, comparing TUR alone with TUR and intravesical chemotherapy in Ta/ T1 superficial bladder cancer.</p>	Tumour recurrence at 1, 2 and 3 years.	<p>11 RCTs; 3,730 patients.</p> <p>Overall analysis found a significant reduction in tumour recurrence at 1 year with intravesical therapy (OR 0.56 95% CI: 0.48 to 0.65 $p < 0.00001$) but the studies exhibited significant heterogeneity.</p> <p>Sub analysis for treatment schedule indicated improved effect with longer schedules.</p> <p>A 2 year schedule with intravesical therapy gave a 73% reduction in tumour recurrence, (OR 0.27 95% CI: 0.19, 0.39, $p = 0.0001$).</p> <p>Mitomycin was the only drug to give a significant reduction in tumour recurrence in the absence of heterogeneity (OR = 0.45).</p>	<p>No trials of BCG therapy were included.</p> <p>No assessment of patient risk for recurrence was included.</p> <p>No search strategy was provided. Only 3 electronic searches were conducted.</p> <p>One investigator screened each search.</p> <p>No analysis of dose was conducted; analysis was limited to the effect of schedule.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLARS was searched from 1960 to 1997. Cancerlit and Current Contents (CD-Rom) were searched. Bibliographies of retrieved studies were scanned. Only English language studies were retrieved.</p> <p><i>Inclusion criteria</i> Published RCTs comparing TUR alone with TUR and intravesical chemotherapy in patients with Ta/ T1 superficial Bladder Cancer.</p> <p><i>Quality assessment</i> Yes</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes</p>
Shelley, 2001. ⁷ UK I	To compare the efficacy of intravesical BCG with mitomycin (MMC) in superficial bladder cancer.	<p><i>Participants</i> Patients with Ta/T1 Bladder cancer.</p> <p><i>Interventions</i> Intravesical BCG of any strain or schedule and intravesical mitomycin.</p> <p><i>Design</i> RCTs.</p>	Time to recurrence. Disease progression. Survival.	<p>27 RCTs were located and of these, 6 were deemed eligible for inclusion in the meta-analysis.</p> <p>1,527 patients were randomised in the six trials. 693 patients were randomised to mitomycin and 834 patients were randomised to BCG.</p> <p><i>Efficacy</i> Overall log hazard ratio for recurrence was 0.022 (variance = 0.76) with significant heterogeneity ($p = 0.001$). This does not indicate any significant difference between agents.</p> <p>Subgroup analysis of high risk patients for recurrence indicated no heterogeneity ($p = 0.25$) and a significant difference in favour of BCG, (log HR 0.371</p>	<p>The sub-group analysis involved small patient numbers.</p> <p>Data for progression and survival were extractable from 2 RCTs only.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> Searches were conducted of databases including MEDLINE, Cancerlit, EMBASE, Healthstar, Bids, Cochrane and DARE.</p> <p>Hand searching of relevant journals was conducted.</p> <p><i>Inclusion criteria</i> Yes</p> <p><i>Quality assessment</i> Yes</p> <p><i>Study details</i> Yes</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
				(variance = 0.01; p = 0.0008). No difference was demonstrated between the agents in terms of disease progression or survival.		<i>Appropriate synthesis of results</i> Hazard ratios were used to compare time to event data.
Shelley, 1999. ⁶ UK I	A meta-analysis to compare the incidence of tumour recurrence following transurethral resection (TUR) alone compared with TUR and intravesical Bacillus Calmette-Guerin (BCG).	<i>Participants</i> Patients with Ta and T1 bladder cancer <i>Interventions</i> All patients had TUR. Patients were randomised to receive intravesical BCG or no further treatment. <i>Design</i> Meta-analysis of published RCTs.	Tumour recurrence. Progression. Survival. Toxicity.	6 RCTs were located and these included data on 585 eligible patients; 304 patients underwent BCG instillation and 281 patients underwent TUR only. The studies investigated four different strains of BCG, doses from 75mg to 180mg, given for lengths of instillation of 1 to 2 hours. In 3 studies, patients were also given concomitant percutaneous BCG. <i>Efficacy</i> Recurrence was less common in patients who had undergone instillation of BCG (12 month Peto OR 0.3, 95% CI: 0.21 to 0.43; log HR -0.83, variance 0.02). This implies a 56% reduction in recurrence with BCG. No evidence of heterogeneity between studies was seen (Q = 9.34, d.f. = 5, p = 0.096). The review could not evaluate the effect of BCG on disease progression or survival. Not all patients were at high risk of progression. Some trials were too short and in some trials crossover treatments preclude analyses of long-term outcomes. <i>Toxicity</i> Main toxicities associated with BCG included cystitis, haematuria and fever.	Considerable variation was seen in BCG dose and schedules.	<i>Review question</i> Yes <i>Literature search</i> MEDLINE was searched from 1966 to 2000; Cancerlit, DARE, Healthstar, BIDS, Cochrane Register of Controlled Trials, EMBASE were also searched and hand searching of the proceeding of ASCO were searched from 1996 to 2000. A search strategy was provided. Translation of non-English articles was undertaken. <i>Inclusion criteria</i> RCTs only were included. Patients with Ta or T1 bladder cancer and who were at medium/high risk for recurrence. <i>Quality assessment</i> Yes <i>Study details</i> Yes <i>Appropriate synthesis of results</i> Peto odds ratio, hazard rates.

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Smith, 1999. ⁵ USA I	To make practice recommendation for non-muscle invasive bladder cancer.	<p><i>Participants</i> Patients with non-muscle invasive bladder cancer (Ta, T1 and Tis).</p> <p><i>Interventions</i> Intravesical therapy and transurethral resection.</p> <p><i>Design</i> Trials comparing TUR alone with TUR and intravesical therapy or comparing intravesical agents following TUR.</p>	Probability of tumour recurrence, tumour progression and complications of treatment.	<p>Data were extracted from 181 reports which detailed 30 RCTs and 151 case control series.</p> <p><i>Efficacy</i> All intravesical agents resulted in lower probability of recurrence compared with TUR alone. However, there was no evidence that intravesical therapy affects long-term progression.</p> <p><i>Toxicity</i> Local bladder symptoms were the most common side-effects – dysuria, frequency, urgency, pain and haematuria. More severe systemic complications included flu-like symptoms and infections.</p>	<p>The confidence profile method for the meta-analysis of recurrence, progression and complications was used.</p> <p>Each intravesical agent (thiotepa, BCG, mitomycin, doxorubicin) was compared with TUR alone and to each other.</p> <p>Only one database searched and only English language studies were included.</p> <p>No search strategy was given.</p> <p>No data extraction details or no citations of included trials were given. Data from non-RCTs were combined with data from the RCTs for complications analysis.</p> <p>Expert panel opinion influenced the interpretation of the evidence.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature Search</i> MEDLINE was searched from 1966 to 1998.</p> <p><i>Inclusion criteria</i> Not stated.</p> <p><i>Quality assessment</i> Yes</p> <p><i>Study details</i> None given.</p> <p><i>Appropriate synthesis of results</i> Bayesian statistics.</p>



Table 8.1b: Superficial bladder cancer: RCTs

Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods
Oosterlinck, 1993. ¹⁰ Belgium, The Netherlands II	To compare the efficacy of a single intravesical instillation of epirubicin to water in Ta and T1 carcinoma of the bladder.	<p><i>Participants</i> 431 eligible patients with solitary, primary or recurrent Ta or T1 transitional carcinoma of the bladder, G 1 to 3 and performance status of greater than 2. Patients aged over 85 years of age were excluded. Patients who had received chemotherapy within 12 months of the trial were excluded.</p> <p><i>Interventions</i> All patients underwent TUR. They were then randomised to receive one intravesical instillation of either epirubicin (80mg/50ml physiological solution) or water (50ml). The instillation was carried out within 6 hours of the TUR.</p> <p><i>Design</i> RCT.</p>	<p>Disease-free interval.</p> <p>Recurrence rate.</p> <p>Toxicity.</p>	<p><i>Efficacy</i> Recurrence: At a mean overall follow-up of 23.4 months, 29% of patients who had been treated with epirubicin and 41% of patients who had been treated with water had developed recurrence ($p < 0.0001$).</p> <p>The recurrence rate among the patients with primary disease treated with epirubicin was 0.15 recurrences per year and among such patients treated with water the recurrence rate was 0.31 recurrences per year ($p < 0.0001$).</p> <p>The recurrence rate among the patients with primary disease treated with epirubicin was 0.26 recurrences per year and among such patients treated with water the recurrence rate was 0.35 recurrences per year ($p < 0.38$).</p> <p><i>Toxicity</i> 24 patients treated with epirubicin and 4 patients treated with water had chemical cystitis and 2 patients who had been treated by epirubicin had skin allergy.</p> <p>No haematological toxicities were noted.</p>	This report details a small study.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes. The Kaplan Meier method was used in conjunction with the log rank test.</p>

Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods
Tolley, 1996. ¹¹ UK II	To test the effectiveness of a single intravesical instillation of mitomycin in reducing tumour recurrence after TUR for superficial bladder cancer.	<p><i>Participants</i> Patients with newly diagnosed Ta or T1 transitional carcinoma of the bladder.</p> <p><i>Interventions</i> Following TUR, patients were randomised to either no instillation (control), one instillation of mitomycin (group 1) or 5 installations of mitomycin (group 2). Installations of mitomycin consisted of 40mg in 40ml of water.</p> <p><i>Design</i> RCT.</p>	<p>Interval to first recurrence</p> <p>Recurrence rate (number of positive cystoscopies per year)</p> <p>Progression-free interval rate</p>	<p>502 patients entered but data on only 452 patients were analysed.</p> <p><i>Efficacy</i> The results provide evidence that 1 installation of mitomycin decreases the risk of recurrence by 34% (p = 0.01) and that 5 installations of mitomycin decrease the risk by 50% (p = 0.0001).</p> <p>The annual rate of recurrence was 0.82 for patients in the control group, 0.42 for patients in group 1 and 0.31 for patients in group 2. The difference between Group 1 and controls was significant (p < 0.001); as was the difference between Group 2 and the control group (p = 0.001).</p> <p>There was a 26% reduction in recurrence among patients treated with 5 installations as compared with those treated with one instillation. This trend did not however reach statistical significance (p = 0.10).</p> <p>There was no evidence of a difference between groups for progression-free interval or overall survival.</p>	More than one instillation may be beneficial.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Allocation was by sealed envelopes. These were stratified by centre and used permuted blocks.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes. Kaplan Meier with log rank. All 'p' values were 2 sided from a χ^2 distribution on 1 degree of freedom.</p>
Whelan, 2001. ¹² UK II	To estimate the effect of post operative bladder irrigation on the outcome of superficial bladder cancer.	<p><i>Participants</i> 866 patients with newly diagnosed pTa or pT1 transitional cell carcinoma of the bladder; patients were recruited from 18 UK centres.</p> <p><i>Interventions</i> All patients received TUR. Patients were then randomised to receive post-operative glycine irrigation (n = 427) or no irrigation (n = 439).</p> <p><i>Design</i> RCT.</p>	<p>The primary endpoint was the time to first recurrence.</p> <p>A secondary endpoint was overall survival and side effects.</p>	<p><i>Efficacy</i> At 5 years, there was a 6% reduction in the probability of recurrence in the irrigation group (HR 0.83, p = 0.05).</p> <p>There was no significant difference between the two groups in terms of overall survival (p = 0.4).</p> <p><i>Toxicity</i> There was one case of increased frequency in each arm and one case of infection in the irrigation arm.</p>	<p>This was a large multicentre study.</p> <p>The study was presented in abstract form only.</p>	<p><i>Randomisation</i> Yes. All patients were randomised to receive TUR and then irrigation or no irrigation.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Very little methodological info was presented in this short abstract.</p>



Table 8.2a: Muscle-invasive bladder cancer - surgery compared with radiotherapy: systematic reviews:

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Huncharek, 1998, ¹⁴ USA I	To compare pre-operative radiation and cystectomy with cystectomy alone in muscle invasive bladder cancer.	<p><i>Participants</i> Patients with muscle invasive bladder cancer.</p> <p><i>Interventions</i> Arm A consisted of pre-operative radiotherapy at a dose range of 20Gy to 54Gy in standard fractionation schemes (4 out of 5 RCTs) followed by cystectomy. Arm B consisted of cystectomy alone.</p> <p><i>Design</i> Meta-analysis of RCTs.</p>	3 and 5 year survival.	<p>4 RCTs had 5 year survival data covering 751 patients. No heterogeneity was detected (Q = 4.56).</p> <p><i>Efficacy</i> A non-significant benefit to pre-operative radiotherapy (Arm A), (OR 0.71, 95% CI: 0.48 to 1.06).</p> <p>One trial was omitted owing to a major failure (> 50%) to deliver the treatment to which participant patients had been randomised and the remaining results were re-analysed.</p> <p>This re-analysis of the remaining studies gave a similar result (OR = 0.94, 95% CI: 0.57 to 1.55).</p> <p>3 year survival data was available for all 5 studies and again a non-significant effect was noted (OR 0.91, 95% CI: 0.64 to 1.30).</p>	<p>No information on the T-stage of the participating patients was given.</p> <p>No details on cystectomy technique were given.</p> <p>No analysis of morbidity was conducted.</p> <p>Limited information on search strategy was given.</p> <p>No data on radiation fractionation schedules were given.</p> <p>A small number of patients were included.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature Search</i> MEDLARS, 1970 to 1997, Cancerlit, EMBASE, Current Contents.</p> <p><i>Inclusion criteria</i> RCTs only.</p> <p><i>Quality assessment</i> Yes</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Data analysed using Peto Odds ratio. Test of heterogeneity calculated.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Shelley, 2001. ¹³ UK I	To compare radical surgery compared with radical radiotherapy in patients with muscle invasive bladder cancer.	<p><i>Participants</i> Patients with muscle invasive bladder cancer stages T2 to T4a.</p> <p><i>Interventions</i> Arm A consisted of pre-operative radiotherapy (40Gy to 50Gy in 20 to 25 daily fractions, each of 2Gy per fraction and lasting 4 to 5 weeks) and radical cystectomy. Arm B consisted of radical radiotherapy (total dose 60Gy to 70Gy in 30 to 35 fractions of 2Gy per fraction given over 6 to 7 weeks) and salvage cystectomy.</p> <p><i>Design</i> Reanalysis of RCTs.</p>	Overall survival at 3, 5 and 10 years. Disease specific. Survival at 3 and 5 years. Morbidity.	<p>3 RCTs, including 439 patients, were included. 221 patients were randomised to Arm A and 218 patients who were randomised to Arm B.</p> <p>The mean overall survival, analysed on an intention to treat basis, at 3 years was 45% for patients who were randomised to Arm A and 28% for patients who were randomised to Arm B (OR 1.19; 95% CI: 1.30 to 2.82).</p> <p>When a 'treatment received' analysis was performed, those patients who were randomised to Arm A had higher survival than those who were randomised to Arm B (OR 1.84; 95% CI: 1.17 to 2.90).</p> <p>The mean overall survival, analysed on an intention to treat basis, at 5 years was 36% for patients who underwent cystectomy and 20% for patients who were randomised to Arm B (OR 1.85; 95% CI: 1.22 to 2.82).</p> <p>When a 'treatment received' analysis was performed, those patients who were randomised to Arm A had higher survival than those who were randomised to Arm B (OR 2.17; 95% CI: 1.39 to 3.38).</p> <p>Disease specific survival was significantly improved among patients who were randomised to Arm A when a treatment-received analysis was used (OR 1.96; 95% CI: 1.06 to 3.65).</p> <p>The results suggest survival benefit with pre-operative radiotherapy and radical cystectomy compared with radical radiotherapy and salvage cystectomy.</p>	<p>The review was based on only 3 RCTs.</p> <p>A small number of patients were included. Improvements in both radiotherapy and surgery have been made since the initiation of included studies.</p> <p>The report was a re-analysis of published reports; the authors did not attempt an Individual Patient Data analysis.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature Search</i> MEDLINE, Cancerlit, Healthstar, Cochrane, DARE, EMBASE. Authors were contacted.</p> <p><i>Inclusion criteria</i> RCTs.</p> <p><i>Quality assessment</i> Yes</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes. Odds ratios and tests for heterogeneity were calculated.</p>



Table 8.2b: Muscle-invasive and locally advanced bladder cancer: primary studies.

Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods								
Duchesne, 2000. ¹⁹ UK Australia Norway II	To compare the efficacy and toxicity of two hypo-fractionated radiotherapy schedules for the palliation of local symptoms from muscle invasive bladder cancer.	<p><i>Participants</i> Patients with confirmed symptomatic muscle invasive bladder cancer causing local symptoms, unsuitable for chemotherapy or radical radiotherapy.</p> <p>Data were available on 272 patients (500 patients recruited).</p> <p>Pre-treatment assessment included cystoscopy and resection to provide confirmation of diagnosis and staging.</p> <p><i>Interventions</i> Patients were randomised to 35Gy in 10 fractions over two weeks or 21Gy in 3 fractions on alternate weekdays over one week.</p> <p>Patient were assessed approximately 2 weeks after the end of radiotherapy and 3 months from the start of the treatment course.</p> <p><i>Design</i> RCT.</p>	Overall symptomatic improvement Survival. Quality of life.	<p>500 patients were recruited; of these 363 patients were male and 137 patients were female.</p> <p>At 3 months post therapy, cystoscopic assessment was conducted on 70 patients. 45% of the patients who had been randomised to the 35Gy treatment arm had tumour present while 62% of the patients who had been randomised to receive 21Gy had evidence of tumour on cystoscopy. This difference was not statistically significant.</p> <p>An overall similar distribution for cause of death was seen in both arms of the study.</p> <p>Overall symptomatic improvement at the end of treatment was 53% for patients treated with 35Gy compared with 50% of those patients treated with 21Gy (difference = 3%, 95% CI: -6% to 12%; p = 0.421).</p> <p>An overall improvement in symptoms was seen at 3 months in 71% of patients treated with 35Gy as compared with 64% of patients treated with 21Gy (difference = 7%, 95% CI: = 2% to 13%; p = 0.421).</p> <p>Pooling data from each arm, symptom specific improvements at 3 months were as follows:-</p> <table border="0"> <tr> <td>Haematuria</td> <td>88%</td> </tr> <tr> <td>Frequency</td> <td>82%</td> </tr> <tr> <td>Dysuria</td> <td>72%</td> </tr> <tr> <td>Nocturia</td> <td>64%.</td> </tr> </table> <p>The median time to deterioration of bladder-related symptoms from the start of radiotherapy was 9 months.</p> <p>No evidence of differences in the performance statuses achieved by patients randomised to the two arms was demonstrated (p = 0.835).</p> <p>No evidence of a difference in quality of life indicators of patients randomised to the two arms was demonstrated.</p>	Haematuria	88%	Frequency	82%	Dysuria	72%	Nocturia	64%.	<p>The use of 21Gy in 3 fractions appears as effective as 35Gy in 10 fractions although slight differences in survival, symptomatic improvement rates and toxicity can be excluded</p>	<p><i>Randomisation</i> Multicentre RCT.</p> <p>Patients were stratified by centre.</p> <p><i>Allocation concealment</i> Permuted blocks method of randomisation used.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> An intention to treat analysis was used.</p> <p>The χ^2 test was used to assess interactions.</p> <p>Quality of life symptoms were assessed using the Mann Whitney U test.</p>
Haematuria	88%													
Frequency	82%													
Dysuria	72%													
Nocturia	64%.													

Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods
Edsmyr, 1985. ¹⁸ Sweden II	To determine the efficacy of hyper-fractionated radiotherapy compared with conventional radiotherapy for locally advanced bladder cancer.	<i>Participants</i> 168 patients with T2 to T4 bladder carcinoma. <i>Intervention</i> Patients were randomised to receive either conventional radiotherapy of 2Gy once a day to a total of 64Gy or hyperfractionated radiotherapy of 1Gy 3 times a day to a total dose of 84Gy. <i>Design</i> RCT.	Local tumour control. Survival. Toxicity.	<i>Local tumour control</i> The relative value of tumour clearance by cytology and cystoscopy, significantly favoured patients treated with hyper-fractionated radiotherapy to a dose of 84Gy (p = 0.051 to p < 0.001). <i>Survival</i> Survival was significantly improved among patients with T3 lesions treated with hyper-fractionated radiotherapy to a dose of 84Gy (p < 0.01). <i>Toxicity</i> Bowel complications requiring surgical treatment were observed in 10 patients treated with hyper-fractionated radiotherapy to a dose of 84Gy compared with 4 patients treated with normally fractionated radiotherapy to a dose of 64Gy.	The conventional group included a 2 week gap and the local control rate might, therefore, have been compromised.	<i>Randomisation</i> Yes <i>Allocation concealment</i> Not stated. <i>Completeness of patient data</i> Yes <i>Appropriate analysis of results</i> Yes. Life table analysis was applied to data and compared with the log rank test.
Mommsen 1989. ²⁰ Scandinavia II	To determine quality of life (QoL) in a randomised study comparing cystectomy with radical radiotherapy.	<i>Participants</i> Men and women treated for deeply invasive bladder cancer (T2 to T4). <i>Interventions</i> Patients were randomised to either pre-operative radiotherapy (40Gy) followed by cystectomy (Arm A) or to radical radiotherapy (60Gy) with salvage cystectomy (Arm B). Patients were mailed a quality of life questionnaire at 6 months and also <i>Design</i> RCT.	Physical condition. Psychological condition. Working capacity. Income. Relation to family and friends. Information received concerning treatment.	<i>Questionnaire at six months</i> 107 patients responded to the questionnaire. There were more complaints of fatigue in the patients randomised to Arm A. More patients in Arm A needed help at home owing to their urostomy. More patients randomised to Arm B felt drug expenses to be heavy. In the case of other questions there were no significant differences between the groups. <i>Questionnaire at 12 to 18 months</i> 68 patients responded to the questionnaire. No significant differences were found between the treatment groups, except that all cystectomised men had erectile impotence. In the group who had received radical radiotherapy, 36% of men were impotent. Significantly more patients in Arm A said that normal coitus could not be carried out (96% compared with 59%).	This study does not allow any final conclusion concerning differences in QoL, between cystectomy and radiotherapy. There was a clear difference in the incidence of impotence.	<i>Randomisation</i> Yes <i>Allocation concealment</i> Not stated <i>Completeness of patient data</i> Yes. The percentage of patients returning their questionnaires in the cystectomy group and the radiotherapy group were, respectively, 82% against 70% for questionnaire 1 and 74% against 55% for questionnaire 2. <i>Appropriate analysis of results</i> Details of the trial itself are given in DAVECA protocol 8201. ³⁹

Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods								
Bell, 1999. ¹⁵ UK VI	To assess the efficacy and safety of definitive external beam radiation (EBRT) in the treatment of invasive bladder cancer.	<p><i>Participants</i> Patients with transitional cell carcinoma of the bladder undergoing EBRT for curative intent.</p> <p><i>Interventions</i> EBRT (40Gy to 65Gy in a median 20 fractions).</p> <p><i>Design</i> Retrospective analysis of patients notes over 8 year period.</p>	Toxicity. Survival.	<p>Data from 120 patients were obtained and analysed (109 men, median age 70 years).</p> <p><i>Tumour Staging</i></p> <table> <tr> <td>T1</td> <td>16%</td> </tr> <tr> <td>T2</td> <td>43%</td> </tr> <tr> <td>T3</td> <td>38%</td> </tr> <tr> <td>T4</td> <td>3%</td> </tr> </table> <p><i>Efficacy</i> 67 of 120 patients (59%) developed local recurrence; of these, the recurrence in the cases of 36 patients (45% of recurrences) were invasive.</p> <p>The overall median survival was 60 months. 33 patients underwent salvage cystectomy with a subsequent median survival of 12.5 months.</p> <p><i>Toxicity</i> Overall morbidity at 12 months was 12%; this consisted of proctitis 8% or cystitis 4%.</p>	T1	16%	T2	43%	T3	38%	T4	3%		<p><i>Sample</i> Pass</p> <p><i>Inclusion/exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>
T1	16%													
T2	43%													
T3	38%													
T4	3%													

Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods
Hayter, 1999. ¹⁶ Canada VI	To report on the use and outcome of radical radiotherapy in invasive bladder cancer.	<p><i>Participants</i> Patients who received radical radiotherapy for bladder cancer. Identified from Ontario Cancer Registry 1982 to 1994.</p> <p><i>Interventions</i> Radical radiotherapy or curative intent (or dose of greater than 39.5Gy if intent missing).</p> <p><i>Design</i> Retrospective population registry based study.</p>	<p>Overall and cause-specific survival.</p> <p>Bladder preservation rate.</p>	<p>20,906 cases of bladder cancer were identified from the database; of these 1,372 cases were identified which meet the inclusion criteria.</p> <p>The mean age at diagnosis was 69.8 years for patients undergoing radical radiotherapy compared with 64.7 years for those having total cystectomy (p = 0.001).</p> <p><i>Radical radiotherapy</i> The most common dose/fractionation schedule was 60Gy/30 fractions. The use of radiotherapy for initial management of bladder cancer declined over the period of the study (from 7.7% to 5.7%, p = 0.001).</p> <p>The median time from diagnosis to radical radiotherapy increased from 10.4 weeks (1982 to 1985) to 15.6 weeks (1990 to 1994). Median time from diagnosis to radical radiotherapy was 11.0 weeks (for non-papillary TCC) and 19.3 weeks (for papillary TCC).</p> <p><i>Survival</i> Median follow-up was 25.1 months. 663 of 903 deaths were owing to bladder cancer. Cause-specific survival at 5 years was 41.3%. Overall survival at 5 years was 28.2%.</p> <p>Squamous or non-papillary histology and age over 70 years were associated with poorer survival at 5 years.</p> <p>Cystectomy-free survival at 5 years following radical radiotherapy was 24.8%.</p> <p>Median time to salvage cystectomy following radiotherapy was 10.0 months. Non-papillary histology and over 70 years associated with increased risk of death within 5 years of salvage total cystectomy.</p> <p>Median follow-up from salvage cystectomy was 19.3 months. The cause-specific and overall survival following salvage cystectomy were 35.7% and 28.1% respectively.</p>	<p>A large number of patients were studied although patients may have been a selected sub-population.</p> <p>The radiotherapy dose was low by modern standards</p> <p>Better planning technology is now available</p> <p>No treatment related complications were reported.</p> <p>Cases were identified from electronic records of Ontario Cancer registry and linked to surgical records from all Ontario hospitals and radiotherapy records from all Ontario cancer centres.</p>	<p><i>Sample</i> Pass</p> <p><i>Inclusion/Exclusion Criteria</i> Pass</p> <p><i>Entry Point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub Series</i> N/A</p>



Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods
Stein, 2001. ¹⁷ UK VI	To determine the long-term treatment effects of radical cystectomy and pelvic lymph node dissection in patients with invasive bladder cancer.	<p><i>Participants</i> All patients with transitional cell carcinoma of the bladder. 80% (n = 843) were male and 20% (n = 211) were female. The median age was 66 years (Range: 22 to 93)</p> <p><i>Interventions</i> Radical cystectomy with bilateral pelvic iliac lymph-adenectomy. Adjuvant therapies were also evaluated (radiation and/or chemotherapy).</p> <p><i>Design</i> Retrospective. All patients were followed post-operatively at 4 month intervals for the first year and at 6 monthly intervals for the second year and annually thereafter.</p>	<p>Perioperative death</p> <p>Recurrence free survival.</p> <p>Time to recurrence.</p>	<p>1,054 patients were analysed. 27 (3%) perioperative death occurred.</p> <p><i>Efficacy</i> No obvious difference in mortality was observed in patients undergoing different urinary diversions or the administration of different perioperative therapy. Most deaths which occurred within the first three years of cystectomy were attributed to bladder cancer. After three years cause of death could be mainly attributed to other unrelated diseases. Overall survival for all patients was 66% at five years. Recurrence-free survival at 5 years was 68%. Overall survival at ten years was 43% and the recurrence-free survival rate was 60%. 311 patients (30%) developed recurrent disease. The median time to the development of the recurrence was 12 months (range 0.04 years to 11.1 years). 234 patients (22%) developed distant recurrence and 77 patients (7%) developed local pelvic recurrence. Increasing pathologic stage and the extent of lymph node based disease were associated with significantly higher recurrence rates and worse overall survival $p < 0.001$.</p> <p><i>Toxicity</i> 83 of 278 patients (30%) experienced early complications. Again no obvious differences were recorded in the different urinary diversion and peri-operative therapy groups.</p>	<p>Large series of patients. Long-term follow-up. Quality of life issues considered. Based on database information rather than patient randomisation. Based on an analysis of a computerised cystectomy database containing clinical and pathological information for all patients who have undergone cystectomy since August 1971.</p>	<p><i>Sample</i> Pass</p> <p><i>Inclusion/exclusion criteria</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

Table 8.3a: Invasive bladder cancer - neo-adjuvant and adjuvant chemotherapy: systematic reviews

Study Country Grade	Aims of Study	Included studies	Outcomes	Results	Comments	Methods
Advanced Bladder Cancer Overview Collaboration, 1999. ²¹ UK, Canada, USA, Spain I	To determine whether neo-adjuvant or concurrent platinum-based chemotherapy improves the survival of patients with locally advanced bladder cancer.	<p><i>Participants</i> Patients with advanced bladder cancer.</p> <p><i>Interventions</i> All patients in included studies received local treatment. Patients were randomised to receive either cisplatin-based radiotherapy or no further therapy.</p> <p><i>Design</i> An individual patient data meta-analysis (IPD).</p>	Patient survival.	<p>Individual patient data (IPD) were available from 4 of 5 trials. In respect of the fifth trial, results were estimated by means of the sum of the hazard ratio (HR) and the standard error (SE). This estimator was used to supplement data from the other trials).</p> <p>Of the four trials from which with full data sets were obtainable, data on 479 patients were extracted.</p> <p>Patients in 3 trials completed chemotherapy before starting local therapy and one gave chemotherapy simultaneously with radiotherapy or with radiotherapy and cystectomy.</p> <p>The evidence from the IPD analysis did not demonstrate that chemotherapy offers any benefit over local therapy alone in terms of survival: HR 1.02 (95% CI: 0.81 to 1.26, p = 0.845)</p> <p>Incorporating the statistics derived from the fifth trial also failed to show any significant advantage for either treatment arm; HR 0.91 (p = 0.32895% CI: 0.75 to 1.10).</p>	<p>Well conducted meta-analysis of available data.</p> <p>The analysis may benefit from an update to incorporate data from four trials which have been published since the analysis was conducted</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE and Cancerlit were searched in 1992. Hand searching of reference lists of relevant studies, meeting abstracts and the PDQ database was conducted. Searches re-done in 1999 using the Cochrane search strategy.</p> <p><i>Inclusion criteria</i> RCTs comparing local treatment with same treatment and chemotherapy.</p> <p><i>Quality assessment</i> Yes</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Intention to treat (ITT) analysis based on individual patient data.</p>



Study Country Grade	Aims of Study	Included studies	Outcomes	Results	Comments	Methods
Dimopoulos, 1998. ²² Greece I	To evaluate the effectiveness of adjuvant and neo-adjuvant chemotherapy for muscle-invasive bladder cancer.	<p><i>Participants</i> Patients with muscle-invasive bladder cancer with or without organ-confinement.</p> <p><i>Interventions</i> Adjuvant or neo-adjuvant chemotherapy, radical cystectomy, radical radiotherapy or trans-urethral resection of the bladder tumour (TURBT).</p> <p><i>Design</i> Systematic review of RCTs.</p>	Disease-free survival. Overall survival.	<p><i>The role of post-operative chemotherapy</i> Four RCTs were included which compared radical cystectomy with radical cystectomy and post-operative chemotherapy. The total number of patients was 267.</p> <p>Three studies showed a significant increase in the time to progression in the chemotherapy arm and two showed significant increase in survival or disease-free survival for the patients who had been randomised to chemotherapy. The review was unable to establish an undisputed benefit of post-operative chemotherapy. Any benefit may, in fact, be restricted to patients with lymph-node involvement.</p> <p>Studies were difficult to interpret owing to small numbers, premature termination and a lack of compliance. The review did not demonstrate support for the use of chemotherapy in organ-confined disease.</p> <p><i>The role of post-irradiation chemotherapy</i> Two RCTs compared radical radiotherapy with radical radiotherapy and post-irradiation chemotherapy</p> <p>Neither trial showed a significant benefit to chemotherapy. In each case, agents with limited activity in bladder cancer were used. The data do not support the use of adjuvant chemotherapy following radical radiotherapy.</p> <p>Less than 10% of cases present with non-TCC bladder cancer, but one RCT showed a significant benefit to patients treated with epirubicin in bilharzial SCC.</p> <p><i>Neo-adjuvant chemotherapy</i> Several recent trials have assessed neo-adjuvant chemotherapy or a sequence of chemotherapy and radiotherapy followed by cystectomy. There is some evidence for benefit owing to neo-adjuvant chemotherapy, to be updated with data from two ongoing multicentre trials.</p>	<p>No clear recommendations can be made because many studies are small, contradictory or inadequate.</p> <p>The data on neo-adjuvant chemotherapy may be useful when updated.</p> <p>Little methodological information was presented.</p> <p>No RCTs are available that assess adjuvant chemotherapy following TURBT. No recommendation can be made based on Phase II trials.</p> <p>No prospective studies specifically address adjuvant chemotherapy following radical cystectomy.</p> <p>Only recent data were reported in this review.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE was searched and a manual search of Index Medicus was conducted. Other searches were not specified.</p> <p><i>Inclusion criteria</i> No details.</p> <p><i>Quality assessment</i> No details.</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> No formal meta-analysis has been carried out, because the studies could not be pooled.</p>

Table 8.3b. Advanced bladder cancer-neo-adjuvant, adjuvant and concurrent chemotherapy: RCTs.

Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods
Coppin, 1996. ²⁶ Canada II	To determine if the addition of concurrent cisplatin to preoperative or definitive radiotherapy improves local control or survival in muscle-invasive bladder cancer.	<p><i>Participants</i> Patients with T2 to T4b transitional cell carcinoma of the bladder, pre-selected for either definitive radiotherapy or pre-operative radiotherapy and cystectomy.</p> <p><i>Interventions</i> Local therapy consisting of either preoperative radiotherapy followed by cystectomy or definitive radiotherapy was chosen before randomisation.</p> <p>All patients received radiation (40Gy) to the whole pelvis and were randomised to receive concurrent cisplatin (100mg/m² x 3, every 2 weeks or no cisplatin.) Patients then proceeded to the consolidated plan of definitive radiotherapy (boost of 20Gy) or cystectomy.</p> <p><i>Design</i> RCT.</p>	<p>Clinical response; complete (CR), residual cancer (RC) and progressive disease (PD).</p> <p>Pelvic relapse rates.</p> <p>Progression-free survival.</p> <p>Overall survival.</p>	<p>99 eligible patients were randomised to receive concurrent cisplatin (51) or to the control arm (48). Patients were stratified by radiation dose and radiation plan.</p> <p>78% (40) of patients randomised to cisplatin received the full 3 courses. No patients in the control arm received chemotherapy before relapse.</p> <p>All patients randomised to receive pelvic radiotherapy completed radiotherapy as planned. 4 patients failed to complete definitive (boost) radiation and 3 did not undergo planned cystectomy.</p> <p>A complete response was seen in 24 of 51 patients on cisplatin and 15 of 48 in control arm (difference = 16%; 95% CI: -5% to 37%, p = 0.16). There were fewer failures of any type in cisplatin arm (29/51 compared with 36/48; p = 0.082).</p> <p>25 of 48 patients in the control group and 15 of 51 patients randomised to receive chemotherapy had their first recurrence in the pelvis (p = 0.036).</p> <p>No difference was demonstrated in the rates of distant metastases between the research groups.</p> <p>After a median follow-up of 6.5 years, 66 patients had died and 57 of these had died from bladder cancer.</p> <p>The 3 year overall survival rates were 47% for patients treated with chemotherapy and 33% for patients randomised to the control group (p = 0.34 using a two sided log rank test). Following and adjustment for prognostic factors (stage and absence of leukocytosis), a similar analysis did not yield a significant difference in survival (HR 0.75; CI: 0.50 to 1.12).</p> <p>Progression-free survival was significantly improved by cisplatin (p = 0.038). At 2 years, 33% of patients on cisplatin had pelvic relapse compared with 53% of patients in the control arm, at 5 years the respective values were 40% and 59%.</p> <p>Improved local control, as reflected in bladder preservation, was seen in 52 patients who elected to receive definitive radiotherapy.</p>	<p>If pre-op, low dose radiotherapy is ineffective, inclusion of these patients could have further diluted an effect.</p> <p>This hypothesis needs to be further tested.</p> <p>The study was relatively small and of limited power.</p> <p>The trial closed before target patient number were achieved.</p>	<p><i>Randomisation</i> Multicentre RCT.</p> <p>Patients were stratified by elected radiotherapy plan.</p> <p><i>Allocation concealment</i> Randomisation conducted by Clinical Trials Group of the National cancer Institute of Canada.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Intention to treat analysis was used.</p> <p>Fischer's exact test was used for categorical parameters. Kaplan-Meier estimates were used for time-to-event data and compared with log-rank and generalised Wilcoxon statistics.</p>



Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods
International Collaboration of trialists, 1999. ²³ International (20 countries) II	To investigate the value of neo-adjuvant cisplatin-based chemotherapy and radical surgery or radiotherapy for muscle-invasive bladder cancer.	<p><i>Participants</i> Patients with T2, G3, T3, T4a, N0 to NX or M0 transitional cell carcinoma of the bladder undergoing curative cystectomy or full-dose external beam radiotherapy.</p> <p><i>Interventions</i> Patients were randomly assigned to no chemotherapy or to three cycles of neo-adjuvant chemotherapy, which consisted of methotrexate, vinblastine and cisplatin with folinic acid rescue.</p> <p>Patients then continued to either pre-planned cystectomy or radiotherapy (non-randomised).</p> <p><i>Design</i> RCT.</p>	<p>Loco-regional persistence or relapse of tumour.</p> <p>Appearance of distant metastases.</p> <p>Survival.</p> <p>Cause of death.</p>	<p>Overall recruitment was 976 patients from 106 institutions in 20 countries. Of these, 491 patients were randomised to receive neo-adjuvant chemotherapy and 485 patients were randomised to receive no neo-adjuvant therapy.</p> <p>Median follow-up 4 years.</p> <p><i>Efficacy</i> A 15% decrease in the overall risk of death in patients treated with chemotherapy was demonstrated ($p = 0.075$).</p> <p>A 21% decrease in the risk of metastasis or death was seen in patients treated with chemotherapy ($p = 0.007$).</p> <p>A 13% decrease in the risk of loco-regional disease or death was seen in patients treated with chemotherapy ($p = 0.087$).</p> <p>An 18% decrease in the risk of loco-regional relapse, metastasis or death was seen in the patients treated with chemotherapy ($p = 0.019$).</p>	A further analysis is expected.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>

Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods
Natale, 2001. ²⁴ USA II	To determine the efficacy of neo-adjuvant M-VAC and cystectomy compared with cystectomy alone in patients with locally advanced non-metastatic bladder cancer.	<p><i>Participants</i> 317 patients with T2 to T4a, N0, M0 transitional cell carcinoma of the bladder.</p> <p><i>Interventions</i> All patients underwent cystectomy. Patients were randomised to receive neo-adjuvant M-VAC, consisting of methotrexate, vinblastine, doxorubicin and cisplatin or to receive no neo-adjuvant therapy.</p> <p><i>Design</i> RCT.</p>	Survival.	<p>307 patients were eligible for inclusion in the trial and of these, 158 patients were randomised to cystectomy alone and the remaining 159 patients received 3 cycles of M-VAC prior to cystectomy.</p> <p>Median follow-up 7.1years.</p> <p><i>Efficacy</i> Survival among patients who received neo-adjuvant therapy was significantly superior to that in the surgery only group (HR 0.74, 95% CI: 0.55 to 0.99, p = 0.027).</p> <p>The estimated median survival time for patients who were randomised to receive chemotherapy was 6.2 years as compared with a median survival time of 3.8 years for patients randomised not to receive chemotherapy.</p> <p><i>Toxicity</i> Grade 4 toxicities occurred in 55 of 150 patients (37%) of patients treated with M-VAC; 50 of these cases presented neutropenia. There were no chemotherapy associated deaths and M-VAC did not affect the severity or incidence of surgical complications.</p>	<p>The data on surgical complications in the M-VAC arm compared with control are not presented.</p> <p>A one-sided test of significance was used.</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis</i> Little methodology information was given. This randomised trial was planned for 298 patients stratified by age and stage.</p>

Study Country Grade	Aims	Study design	Outcome	Results	Comments	Methods
Shipley, 1998. ²⁵ USA II	To assess the efficacy of neo-adjuvant and concurrent chemotherapy in patients with muscle-invasive disease.	<p><i>Participants</i> Patients with cancer of the bladder, stages T2 to T4a NX M0.</p> <p><i>Interventions</i> All patients received 39.6Gy radiotherapy with concurrent cisplatin (100mg/m² in two courses, 3 weeks apart).</p> <p>Patients were randomised to receive no additional treatment or to receive 2 cycles of neo-adjuvant MCV, which consisted of methotrexate, cisplatin and vinblastine.</p> <p><i>Design</i> RCT.</p>	Survival Tumour response (clinical complete response)	<p>123 patients were eligible for entry in the study. 61 patients were randomised to neo-adjuvant therapy while 62 patients received standard therapy only.</p> <p><i>Efficacy</i> 50% of population were alive at the time of the report of the study. 49% of patients treated with neo-adjuvant therapy and 50% of the patients treated with standard chemotherapy and radiotherapy only were alive at the time of reporting.</p> <p>The actuarial 5 year overall survival rate was 49% (with 48% for patients in the neo-adjuvant arm and 49% for patients in the control arm). Actuarial 5 year survival with a functioning bladder was 38% for patients in the neo-adjuvant arm and 40% for patients in the control arm.</p> <p>The complete clinical response rate was 59% overall, 61% for patients in the neo-adjuvant arm and 55% for patients in the control arm.</p> <p>20 patients recurred with either an invasive tumour or a superficial recurrence.</p> <p>Of the 123 patients in the protocol 44% had tumour free bladders with median follow-up of 61 months.</p> <p>Two cycles of MCV were not shown to increase the rate of complete response over that achieved with standard induction therapy or to increase freedom from metastatic disease. There was no impact on 5 year overall survival.</p> <p><i>Toxicity</i> 5 patients died from treatment related causes; of these 4 patients were randomised to neo-adjuvant therapy and 1 patient was randomised to receive standard therapy only.</p> <p>26 patients who received neo-adjuvant chemotherapy experienced toxicity at grade 3. 9 patients experienced grade 4 toxicity. A lethal combination of leucopenia and sepsis occurred in three patients.</p>	<p>The protocol was prematurely closed owing to an unexpectedly high rate of severe neutropenia and sepsis.</p> <p>71% of planned accrual achieved.</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Kaplan Meier and Pearson's χ^2 test were used.</p>

Table 8.4: Metastatic bladder cancer - chemotherapy: RCTs.

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
De Marino, 2001. ⁵³ Italy II	To evaluate the activity and safety of paclitaxel combined with gemcitabine and cisplatin in patients with advanced bladder cancer.	<p><i>Participants</i> 51 patients with advanced transitional cell bladder cancer, measurable disease and no prior chemotherapy.</p> <p><i>Intervention</i> Patients were randomised to receive Arm A or Arm B.</p> <p>Arm A consisted of paclitaxel (70mg/m²), gemcitabine (1g/m²) and cisplatin (35mg/m² days 1 and 8 every 3 weeks).</p> <p>Arm B consisted of gemcitabine (1g/m² days 1, 8 and 15) and cisplatin (70mg/m² day 2 every 4 weeks).</p> <p><i>Design</i> RCT.</p>	Response rates. Toxicity.	<p>The total number of patients enrolled in the trial was 51; of these 47 were male and 4 were female.</p> <p>37 patients had a performance status of 0 to 1 and 14 patients had a status of 2 to 3.</p> <p>32 patients had locally advanced or retroperitoneal disease and 19 patients had metastatic disease.</p> <p><i>Efficacy</i> The response rate was 40% for patients randomised to Arm A and 46% for patients randomised to Arm B.</p> <p><i>Toxicity</i> 6 patients in Arm A and 1 patient in Arm B refused treatment following toxicity during the first cycle.</p> <p>Overall 178 cycles were given. Grade 3 to 4 leucopenia was observed in 48% of patients in Arm A and in 37% of patients in Arm B. Grade 4 thrombocytopenia was seen in 35% of patients randomised to Arm A and 21% of patients in Arm B.</p>	The combination of paclitaxel, gemcitabine and cisplatin is active in TCC. The addition of paclitaxel seems to increase toxicity without improving responses. A small study.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>
Hillcoat, 1989. ²⁷ USA II	To compare the efficacy of single agent cisplatin with the combination of cisplatin and methotrexate in patients with advanced urothelial tract cancer.	<p><i>Participants</i> Patients with recurrent or metastatic transitional cell cancer of the urothelial tract.</p> <p>Patients were stratified according to prior therapy.</p> <p><i>Interventions</i> Patients were randomised to cisplatin monotherapy (80mg/m² day 1 every 4 weeks) or combination</p>	Response rates. Toxicity. Survival.	<p>108 patients were randomised. 53 patients were randomised to the combination arm and 55 to monotherapy. The maximum follow-up was 2 to 5 years.</p> <p><i>Efficacy</i> Complete response occurred in 5 patients (9%) in each arm. The overall (complete and partial) response rate was 24 of 53 patients (45%) for patients treated with combination therapy and 17 of 55 patients (31%) for those treated with cisplatin monotherapy (p = 0.18).</p> <p>Median survival among patients treated with the combination therapy was 8.7 months compared with 7.2 months for patients treated by cisplatin (log rank p = 0.7).</p> <p>No difference was demonstrated in the relapse-free survival (log-</p>		<p><i>Randomisation</i> Yes. Patients were randomised to two treatment groups.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes, 4 lost to follow-up.</p> <p><i>Appropriate analysis of results</i> Response rates and toxicity were analysed by the Yates' continuity – corrected χ^2 test. The product-limit method was used for</p>



Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
		therapy of (Cisplatin 80mg/m ² day 2 and methotrexate 50mg/m ² days 1 and 15 every 4 weeks). <i>Design</i> Multicentre, RCT.		rank p = 0.8). <i>Toxicity</i> Haematological toxicity (p = 0.01) and mucositis (p = 0.0005) were more frequent among patients treated by combination therapy. Nausea and vomiting were more marked in patients treated with the combination therapy (p =0.06). Three treatment-related deaths were recorded; two deaths occurred in patients who were treated with the combination therapy and one death occurred among patients treated with cisplatin monotherapy.		survival probability and curves were compared with the log rank test and the Wilcoxon-Breslow test.
Logothetis, 1990. ³⁰ USA II	To assess the efficacy of cisplatin, cyclophosphamide and doxorubicin (CI:SCA) compared with methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) in metastatic urothelial cancer.	<i>Participants</i> Patients with measurable metastatic urothelial tumours. <i>Interventions</i> Patients were randomised to receive either CI:SCA or M-VAC chemotherapy. CI:SCA consisted of doxorubicin (50mg/m ² day 2), cyclophosphamide (650mg/m ² day1) and cisplatin (100mg.m ² day 2). M-VAC consisted of methotrexate (30mg/m ² days 1, 15 and 22), vinblastine (3mg/m ² days 2, 15 and 22), doxorubicin (30mg/m ² day 2) and cisplatin (70mg/m ² day 2). <i>Design</i> RCT.	Clinical response. Toxicity. Survival.	110 patients were recruited. <i>Efficacy</i> 46% of patients (range 32% to 62%) who were treated by the CI:SCA regime achieved an overall (complete and partial) response. 65% (range 52% to 77%) who were treated by the M-VAC achieved a response. The difference between response rates achieves statistical significance (p < 0.05). <i>Survival</i> The duration of survival among patients treated with M-VAC (mean 62.6 weeks; median 48.35; range 5.0 to 162.3) was significantly superior the response duration seen in patients who were treated according to the CI:SCA regime (mean, 40.4 weeks; median, 36.1; range 7 to 147.1). <i>Toxicity</i> Toxicities included leucopenic fever, neuropathy, renal, hepatic and gastrointestinal bleeding. There was no significant difference in the frequency of toxic reactions although a trend was seen towards a higher incidence of renal toxicity among patients treated by CI:SCA chemotherapy (41%) as compared with a lower incidence of renal toxicity among patients treated with M-VAC chemotherapy (17%).	The number of patients randomised to each group was not stated. No 'p' value for overall survival. No information was given on the statistical methodology.	<i>Randomisation</i> Yes <i>Allocation concealment</i> Not stated. <i>Completeness of patient data</i> Yes <i>Appropriate analysis of results</i> Kaplan Meier plots of survival.

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Mead, 1998. ⁵¹ UK II	To compare the efficacy of methotrexate and vinblastine (MV) with cisplatin, methotrexate and vinblastine (CMV) in advanced transitional cell carcinoma.	<p><i>Participants</i> Patients with histologically confirmed transitional cell carcinoma of the urothelial tract.</p> <p><i>Interventions</i> Patients were randomised to receive 6 cycles of either MV or CMV.</p> <p>MV consisted of methotrexate (30mg/m² days 1 and 8) and vinblastine (4mg/m² days 1 and 8).</p> <p>CMV consisted of cisplatin (70mg/m² on day 2) and methotrexate and vinblastine (at the same doses as in the MV arm).</p> <p><i>Design</i> Multicentre, RCT.</p>	<p>Clinical response.</p> <p>Disease progression.</p> <p>Overall survival.</p> <p>Toxicity.</p>	<p>214 patients were randomised in the trial; of these, 106 patients were randomised to receive MV and 108 patients were randomised to receive CMV.</p> <p><i>Efficacy</i> 10% of 88 patients with evaluable disease who were treated with CMV chemotherapy had a complete response and a further 36% of patients had a partial response. The overall response rate was 46%.</p> <p>7% of 93 patients with evaluable disease who were treated with MV chemotherapy had a complete response and a further 12% of patients had a partial response. The overall response rate was 19%.</p> <p>34 patients (32%) receiving CMV chemotherapy and 72 patients receiving MV chemotherapy (68%) experienced disease progression.</p> <p>A 32% reduction in risk of death was seen among patients treated with CMV (HR 0.68, 95% CI: 0.51 to 0.90, p = 0.0065). This translated to a 2.5 month improvement in median survival (95% CI: 4.5 to 7 months) and an absolute improvement of 13% in the 1 year survival rate (from 16% to 29%).</p> <p><i>Toxicity</i> 5 treatment related deaths (4%) were seen in patients treated with CMV; no treatment related deaths were seen in the MV arm.</p> <p>19 patients had excessive toxicity with CMV. 5 cases of grade III leucopenia or thrombocytopenia were seen among patients treated with CMV. No patient treated with MV chemotherapy experienced excess toxicity or grade III haematological toxicity.</p> <p>Long-term neurological toxicity was reported in 9 patients receiving CMV but only in 1 patient treated with MV chemotherapy.</p>		<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Randomisation was performed via telephone to the MRC trials office.</p> <p><i>Were all patients accounted for</i> Yes</p> <p><i>Appropriate analysis of results</i> Kaplan Meier plots of survival were compared using the Mantel-Cox log-rank test. Tests for heterogeneity were performed. An intention to treat analysis was used.</p>



Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Millikan, 2001. ³⁴ USA II	To investigate the timing of chemotherapy (M-VAC) with respect to surgery, in advanced urothelial cancer.	<p><i>Participants</i> Patients with high-risk but resectable urothelial cancer. Patients had either invasive disease, clinically extra-vesical disease or involvement of adjacent organs.</p> <p><i>Interventions</i> Patients were randomised to receive adjuvant courses of M-VAC following surgery or to receive 2 neo-adjuvant courses of M-VAC before surgery to be followed by 3 courses of therapy after surgery.</p> <p>M-VAC chemotherapy consisted of methotrexate (30mg/m² days 1, 15 and 22), vinblastine (3mg/m² days 2, 15 and 22), doxorubicin (30mg/m² day 1) and cisplatin (70mg/m² day 1). Chemotherapy was cycled every 28 days.</p> <p><i>Design</i> RCT.</p>	Response. Survival. Toxicity.	<p>140 patients were randomised to the trial. 70 patients were randomised to the neo-adjuvant M-VAC and 70 patients were randomised to the adjuvant M-VAC.</p> <p><i>Efficacy</i> There was no significant difference between the two groups in terms of overall survival (p = 0.54). For all 138 patients with bladder cancer the median overall survival was 4 years; 2 had upper tract primaries.</p> <p>Of the 70 patients randomised to adjuvant chemotherapy, 42 patients (60%) remained disease-free. The influence of the pathological stage was not significant. The presence of nodal disease adversely effects disease-free status (p = 0.01).</p> <p>Of the 70 patients assigned to neo-adjuvant chemotherapy, 39 patients (56%) remained disease-free. 63 patients went on to receive cystectomy. After 2 cycles of M-VAC, 25 patients (40%) had no evidence of residual muscle-invasive disease on resection. Of the 14 patients with pathological involvement of pelvic nodes, 12 patients (86%) relapsed and died of metastatic disease (pN+ compared with pN-, p = 0.001).</p> <p><i>Toxicity</i> 12 patients (9%), 6 in each arm, had therapy- induced deaths. 6 related to complications of chemotherapy, 2 to post-operative myocardial infarction and 4 miscellaneous post-operative complications.</p> <p>Overall, 91 patients (65%) received at least 4 cycles of M-VAC. Receiving both chemotherapy and surgery was reported as difficult. 9 patients who were initially assigned to receive surgery prior to chemotherapy, did not receive chemotherapy and 7 initially assigned chemotherapy prior to surgery did not receive surgery. Inability to complete planned therapy was more prominent in the older patients.</p>	<p>A well-conducted although small RCT.</p> <p>The combination of multi-agent chemotherapy and surgery is active for high-risk urothelial cancer, although no preferred sequence was found.</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Were all patients accounted for</i> Yes</p> <p><i>Appropriate analysis of results</i> Kaplan Meier plots of time-to-event-data were used. The test for comparisons was not stated.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Saxman, 1996. ²⁹ USA II	To determine the efficacy of cisplatin alone or in combination with methotrexate, vinblastine and doxorubicin with advanced bladder cancer.	<p><i>Participants</i> Patients with histologically proven advanced bladder cancer, stratified according to Karnofsky performance score (KPS) and previous radiotherapy.</p> <p><i>Interventions</i> Patients were randomised to receive either single agent cisplatin monotherapy (70mg/m² on day 1) or to receive combination chemotherapy with methotrexate (30mg/m² on days 1, 15 and 22), vinblastine (3mg/m² on days 2, 15 and 22), doxorubicin (30mg/m² on day 2) and cisplatin (70mg/m² on day 2). Courses were repeated every 28 days.</p> <p><i>Design</i> RCT.</p>	Survival. Disease-free survival. Response duration.	<p>255 patients were assessable; of these 122 patients were randomised to receive cisplatin monotherapy and 133 patients received M-VAC.</p> <p>The minimum duration of follow-up was 6 years.</p> <p><i>Efficacy</i> The survival difference between M-VAC and cisplatin remains statistically significant (p = 0.00015). Pre-treatment KPS was a strong predictor of survival (p = 0.000011). Transitional cell patients had significantly longer survival than patients with adenocarcinoma or squamous cell tumours (p = 0.0078). Of the 18 patients with non-transitional cell histology, none survived longer than 2 years. Overall survival deteriorated in the presence of liver metastasis (p = 0.0022) or bone metastasis (p = 0.0032). Multivariable Cox modelling showed treatment, KPS and histology to be significant independent predictors of survival and predict poor outcome despite the use of aggressive chemotherapy. At the 3 year follow-up appointment, 4 patients (3.3%) treated with cisplatin monotherapy and 17 patients (12.8%) treated with combination therapy were alive (8.2% of total population). At the 6 year follow-up appointment, 2 patients (1.6%) treated with cisplatin monotherapy and 9 patients (6.8%) treated with the combination therapy were alive (4.3% of the total population). 5 patients (3.7%) treated by combination therapy and 2 patients (1.6%) treated with Cisplatin were alive and continuously free of urothelial cancer at greater than 6 years from diagnosis. The combination M-VAC therapy showed superiority in terms of response (65% as against the 46% response seen in patients treated with cisplatin monotherapy, p < 0.05) and median survival (48.3 weeks as against the median 36.1 week response seen in patients treated with cisplatin monotherapy, p = 0.003).</p>	M-VAC is superior to cisplatin although the evidence suggests that patients with prognostic factors such as non-transitional cell histology, poor performance status and bone metastases are unlikely to benefit significantly.	<p><i>Randomisation</i> Patients were randomised to two treatment groups.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes, although several were lost to follow-up</p> <p><i>Appropriate analysis of results</i> Survival distributions and response duration were calculated using the Kaplan Meier and log rank tests. Cox proportional hazards models used to assess associations between patient characteristics and survival.</p>



Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Soloway, 1983. ²⁸ USA II	To compare the use of Cisplatin alone to the combination of cisplatin and cyclophosphamide in patients with advanced bladder cancer.	<p><i>Participants</i> Patients with biopsy proven advanced bladder cancer. Patients were stratified into two groups; patients with metastatic or regionally advanced disease and patients with tumour confined to the bladder alone.</p> <p><i>Interventions</i> Patients in Arm 1 received Cisplatin (70mg/m²). Patients in Arm 2 received Cyclophosphamide (750mg/m²).</p> <p><i>Design</i> RCT.</p>	<p>Duration of response.</p> <p>Complete clinical response.</p> <p>Partial clinical response.</p> <p>Disease progression.</p>	<p>109 patients were enrolled in the trial. 50 patients were randomised to Arm 1 (cisplatin alone) and 59 patients were randomised to Arm 2 (cisplatin and cyclophosphamide).</p> <p><i>Efficacy</i> Rates of response varied from 20% for patients in Arm 1 to 11.9% for patients in Arm 2. There were five complete responses and five partial responses among patients who were randomised to Arm 1. 32% of patients in this arm had disease stabilisation. There were three complete responses and four partial responses among patients who were randomised to Arm 1. 33.9% of patients in this arm had disease stabilisation.</p> <p>No statistical significance in response was demonstrated between the two arms.</p> <p>Patients with lymph node and soft tissue disease had higher response rates than patients with pulmonary nodules. Patients with bone or liver metastasis had a decreased chance of response. Patients with performance status of 1 or 2 in Arm 1 had a response rate of 22.6% compared with 15.8% among patients in the same arm with a performance status of 3 or 4.</p> <p>Among patients who had responded, no patient in Arm 1 had progressed at three months. In the combination arm, however, 14.3% of patients progressed.</p> <p>Among patients who had responded, 64.6% patients in Arm 1 had progressed at three months. In the combination arm, however, 57.1% of patients progressed.</p> <p><i>Toxicity</i> Nausea and vomiting was the adverse effect which was most commonly reported. Moderate levels were seen in 25% of patients and severe levels were seen in 8% of patients. Severe nausea and vomiting caused withdrawal by 9 patients.</p> <p>27% of patients in the combination arm required at least one dose reduction to manage adverse events.</p>	<p>Survival was not a primary endpoint.</p> <p>Small study.</p>	<p><i>Randomisation</i> Yes. Patients were randomised by contacting the Statistical Co-ordinating Centre of Collaborative Group after ensuring patients fulfilled the eligibility criteria.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Were all patients accounted for</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Von der Maase, 2000. ³² USA II	To compare gemcitabine and cisplatin with methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) for advanced or metastatic bladder cancer.	<p><i>Participants</i> Patients with Stage IV transitional cell carcinoma of the bladder and no prior chemotherapy or immunotherapy.</p> <p><i>Interventions</i> Patients were randomised to receive standard chemotherapy (M-VAC or methotrexate, vinblastine, doxorubicin and cisplatin) as control or to receive gemcitabine and cisplatin.</p> <p><i>Design</i> RCT.</p>	<p>Survival rate.</p> <p>Time to progression.</p> <p>Time to treatment failure.</p> <p>Tumour response rate.</p> <p>Adverse effects.</p> <p>QoL.</p>	<p>405 patients were randomised; of these 203 patients were randomised to the gemcitabine and cisplatin arm of the study and 202 patients were randomised to M-VAC.</p> <p><i>Efficacy</i> The median overall survival for patients in the M-VAC arm was 14.8 months (95% CI: 13.2 to 16.8) while the median overall survival for the patients in the gemcitabine and cisplatin arm was 13.8 months (95% CI: 12.3 to 15.8 months); (HR 1.04 95% CI: 0.82 to 1.32; p = 0.75).</p> <p>The time-to-progression was similar in each arm. The median time for patients receiving M-VAC was 7.4 months (95% CI: 6.7 to 9.1 months) and the median time was 7.4 months (95% CI: 6.6 to 8.1 months) for patients treated with the gemcitabine and cisplatin regime; (HR 1.05; 95% CI: to 0.85 to 1.30, p = 0.66).</p> <p>The time-to-treatment-failure was similar in each arm. The median time to treatment failure for patients in the M-VAC arm was 4.6 months (95% CI: 3.7 to 5.3 months) and the median time to treatment failure was 5.8 months (95% CI: 4.9 to 6.6 months) for patients treated with the gemcitabine and cisplatin regime (HR 0.89; 95% CI: 0.72 to 1.10, p = 0.27).</p> <p>Overall response rates were similar with 55.0% of patients who were treated with M-VAC chemotherapy and 54.3% of patients who were treated with the gemcitabine and cisplatin regime responding to treatment.</p> <p>The median duration of response was 11.0 months (95% CI: 9.4 to 12.6 months) for those treated with M-VAC and 9.6 months (95% CI: 8.0 to 10.8 months) for those treated with the gemcitabine and cisplatin regime (p = 0.48).</p> <p><i>Toxicity</i> Grade 3 and 4 anaemia was more evident in the gemcitabine and cisplatin arm of the study. This did not, however, lead to a higher transfusion rate.</p> <p>The M-VAC chemotherapy arm resulted in more cases of grade 3 and 4 neutropenia, mucositis, infection and diarrhoea.</p> <p><i>Quality of life</i> The gemcitabine and cisplatin regime was significantly more likely to improve weight by 5% or more.</p>		<p><i>Randomisation</i> Patients were randomised to Gemcitabine and Cisplatin or M-VAC using the Pocock and Simon minimisation method.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Based on intention to treat analysis.</p> <p>The time to event endpoints were calculated using Kaplan Meier and Wilcoxon tests.</p>



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Kidney Cancer

The Questions

- a) How effective is partial nephrectomy in the curative treatment of renal cancer?
- b) How effective is adjuvant therapy in renal cancer?
- c) Is nephrectomy beneficial for patients with advanced or metastatic disease?
- d) How effective are systemic therapies for metastatic disease?

The Nature of the Research Evidence

a) Partial nephrectomy

No published RCTs evaluating the effectiveness of partial nephrectomy in renal cancer have been identified. However, some of the older evidence is summarised in two review articles.^{1,2} A retrospective study evaluated the value of partial nephrectomy in terms of tumour control and complication rate.³ There is an ongoing international randomised trial in Europe and North America, randomising patients with small (< 5cm) single renal tumours and no metastases to radical nephrectomy/limited lymphadenectomy or partial nephrectomy/limited lymphadenectomy. Two non-randomised studies report the outcome of radical surgery in cases of invasion of the vena cava where partial nephrectomy is not indicated.^{4,5}

b) Adjuvant therapy

A systematic review which was located included an assessment of the role of cytokine treatments in the adjuvant therapy of renal cancer²⁰ (Table 9.1a). Three recent primary studies were located⁶⁻⁸ (Table 9.1b). A randomised trial of post-nephrectomy adjuvant BCG with the addition of autologous tumour cells was also identified.⁶ Two other randomised trials were also identified. One trial compared adjuvant interferon with observation following nephrectomy.⁷ The second compared low-dose interleukin-2 with or without autologous tumour-infiltrating lymphocytes (TIL), derived from the nephrectomy specimen.⁸ A European randomised trial comparing interferon, interleukin and 5-FU with observation is ongoing.^{9,10}

The role of adjuvant post-operative radiotherapy has also been reviewed in French practice guidelines based on a literature search.¹¹ This included three RCTs of adjuvant therapy of historic interest dealing, in most cases, with adjuvant immunotherapy.¹²⁻¹⁴

c) Nephrectomy in advanced or metastatic disease

Two randomised trials have examined the benefit of nephrectomy in patients with existing systemic disease^{15,16} (Table 9.2). In both of these studies patients with metastatic renal cancer who were treated with interferon were randomised

to nephrectomy or no nephrectomy. A critical commentary of these two trials has been presented.¹⁷

d) Systemic therapies for metastatic disease

The majority of studies in the systemic therapy of advanced renal cancer have used interferon with or without interleukin-2 and chemotherapy. Three reviews were located¹⁸⁻²⁰ (Tables 9.1a and 9.3a). One systematic review was identified, comparing cytokines with non-cytokine-based therapy in metastatic or locally advanced renal cancer.¹⁸ A meta-analysis of eight trials in advanced renal cell cancer compared regimens including interferon- α with those not including interferon.¹⁹ One review has covered several aspects of systemic therapy, including chemotherapy, immunotherapy and combination programs.²⁰

Eleven additional randomised trials were identified (Table 9.3b). These compared oral tamoxifen compared with interleukin-2 combined with interferon- α 2a and 5-fluorouracil,¹⁰ interleukin-2 compared with interleukin-2 and interferon- α ,²¹ interleukin-2 compared with interferon compared with interleukin-2 and interferon,²² interferon or medroxyprogesterone acetate,²³ interferon alone compared with the interferon and *cis*-retinoic acid,²⁴ standard dose interferon compared with low dose interferon and vinblastine,²⁵ vinblastine alone compared with vinblastine and interferon,²⁶ interleukin-2 with or without 5-fluorouracil,²⁷ interleukin-2 alone compared with a combination of interleukin-2 and interferon²⁸ and interferon- γ compared with placebo in metastatic disease.²⁹ One randomised trial has tested quality of life comparing interferon and vinblastine with the same and medroxyprogesterone acetate.³⁰

Two non-randomised trials report on the efficacy of interferon- α and interleukin-2 and 5-FU.^{9, 31} A retrospective multivariate analysis compared the survival impact of interleukin-2 with matched controls.³² The comparison of systemic chemotherapy and cytokine therapy have been reviewed in a retrospective analysis.³³ In addition, one case-control study of 215 home-based patients treated with interleukin-2 alone or interleukin-2 and interferon with or without 5-fluorouracil was found.³⁴ A phase II study reports on oral capecitabine, interferon- α 2a, interleukin-2 and 13-*cis*-retinoic acid in outpatients³⁵ (Table 9.3c).

Summary of the Research Evidence

a) Partial nephrectomy

There is evidence from observational studies that, in some patients, partial nephrectomy may be associated with disease-free survival over many years duration.^{1, 2} Nephron-sparing surgery is associated with a complication rate of 10%, mainly post-operative haemorrhage, but is effective in reducing local recurrence.³ To date there has been no randomised trial published but the ongoing EORTC/ECOG/SWOG study is still recruiting patients to compare conservative (partial nephrectomy) surgery with radical nephrectomy. For patients with more extensive disease, nephron-sparing surgery is inappropriate and complex surgery may be required including consideration of cardiac bypass techniques.^{4, 5} These techniques have not featured in any randomised trial to date but the observational data confirms that such a procedure may be feasible in selected patients and may result in long-term disease control.

Conclusion

Nephron-conserving surgery is an option for selected patients with small tumours and continues to be the subject of an ongoing trial.

b) Adjuvant therapy

Three randomised trials of adjuvant radiotherapy following nephrectomy concluded that there was no significant clinical benefit in terms of recurrence or survival¹²⁻¹⁴ and one study identified fatal liver toxicity as a complication of radiotherapy for right-sided tumours.¹⁴ This is in agreement with a French practice guidelines report.¹¹

A review of adjuvant cytokine therapy was based on a search for publications between 1990 and December 1998, including both phase II and phase III studies.²⁰ Relapse occurs in 20% to 30% of patients with completely resected renal cell carcinoma after radical nephrectomy and observation remains the standard care since no recognised systemic therapy reduces the likelihood of relapse. No search strategy or quality assessment criteria were included in this review.

In a randomised trial of adjuvant interferon following radical surgery, 264 patients with locally advanced or lymph node metastatic disease were randomised to observation alone or to interferon- α 2b, three times per week for six months.⁷ This trial has not shown a benefit in terms of disease progression or survival except on subgroup analysis of a very small number of pN2/N3 patients.⁷

One trial randomised 120 patients with non-metastatic renal cancer treated by nephrectomy to weekly intradermal BCG or to observation.⁶ There was no difference in disease-free survival or overall survival.

A multicentre randomised study randomised 160 patients following nephrectomy.⁸ Patients were treated with interleukin-2 and a placebo infusion or interleukin-2 and TILs which were extracted from the primary tumour. Only 39 out of 81 patients in whom the intent was to treat with TIL actually received this treatment owing to low yields from the specimen. No differences were seen in median survival rates and the trial was terminated.

Conclusion

There is no evidence that adjuvant radiotherapy improves survival following nephrectomy. To date, no trial has demonstrated any benefit for the use of adjuvant cytokine therapy following nephrectomy.

c) Nephrectomy in advanced or metastatic disease

The SWOG 8949 randomised trial has reported that nephrectomy prior to treatment with interferon improved survival in 241 patients with metastatic renal cancer, from a median of 8.1 months to 12.5 months.¹⁵ A criticism of this study however is that a one-sided test of significance was performed and the number of responders to interferon in patients not undergoing nephrectomy was lower than expected.¹⁷ A second randomised trial of similar design reported on 85 patients.¹⁶ Improvements in the time to progression (5 compared with three months, $p = 0.04$) and median survival (17 compared with seven months,

$p = 0.03$) were seen in the nephrectomy-treated patients. Both studies recruited a relatively small number of patients over a very long time period, leading to the possibility that the patient population may not be representative.¹⁷

Conclusion

The current weight of evidence is in favour of nephrectomy prior to interferon treatment for selected patients presenting with metastatic disease. Many patients in this category are, however, not fit to undergo nephrectomy.

d) Systemic therapies for metastatic disease

There is now high quality evidence that treatment of advanced renal cancer with interferon- α produces a significant survival benefit of a few months duration, in comparison with hormone therapy. These data have been summarised in two systematic reviews,^{18, 19} but the strongest evidence comes from two randomised trials.^{23, 26} In the MRC trial, 335 patients were randomised to 12 weeks of treatment with interferon or to medroxyprogesterone acetate.^{23, 26} There was a 2.5 month improvement in median survival in the interferon-treated patients ($p = 0.017$ for hazard ratios). In a study from Finland, 160 patients were randomised to vinblastine alone or to vinblastine and interferon- α for 12 months or until disease progression.^{23, 26} Median survival was improved from 38 weeks in the vinblastine arm, to 68 weeks in the vinblastine and interferon arm ($p = 0.049$). The optimum dose and schedule of interferon- α has not been defined. However, treatment with interferon is associated with significant toxicity.^{23, 26} In a randomised trial, response rates and survival were not improved by the addition of *cis*-retinoic acid to interferon.²⁴ A randomised trial of 100 patients compared standard dose interferon with a lower dose of interferon- α and vinblastine and reported that the response rates were identical. The toxicity was lower in the low-dose interferon arm.²⁵

The optimum cytokine or combination of cytokines is not defined. A randomised trial in 197 patients compared interferon- γ to placebo but failed to show any improvement in response rates, time to progression or overall survival unlike the interferon- α studies.²⁹ Randomised trials comparing interleukin-2 as the sole cytokine with non-cytokine treatments (i.e. equivalent to the interferon trials described above) have not been performed. However, tentative evidence exists to suggest that a similar effect on survival could occur. In a retrospective review of 670 patients treated in one institution in 24 trials of systemic chemotherapy or cytokine therapy, patients treated with cytokine therapy had a longer survival time than those treated with chemotherapy.³³ A similar conclusion was reached from a retrospective, multivariate analysis of 387 patients who were compared with 390 matched controls.³² Around 5% of patients treated with cytokines appear to have durable complete remissions.³³

This must be weighed against the observation of spontaneous responses, including spontaneous complete remissions, in untreated patients.²⁹ It may be that spontaneous remissions are less common than durable complete remissions after cytokines, but this has not been tested formally. Surgical excision of isolated metastases has also been associated with long-term disease control.^{20, 33}

In an RCT comparing interleukin-2, interferon- α or both, 425 patients with metastatic renal cancer were randomised. The highest response rates were seen with the combination treatment (response rate = 18.6%) compared with 6.5% for

interleukin-2 and 7.5% for interferon respectively ($p < 0.01$). There were however no differences in overall survival between the three groups.²² The addition of interleukin-2 to interferon increased the toxicity of treatment. An Italian study with a similar design also failed to show a survival benefit for combination treatment. However, again, response rates were highest for the combination of interleukin-2 and interferon and complete responses were only seen in interleukin-2 treated patients.²⁸ No differences in response or survival were seen in 60 patients randomised to interleukin-2 alone or to interleukin-2 and interferon and only two partial responses were seen, with no complete responders. Toxicity was more marked with the combination.²¹

The three-drug combination of interferon- α , interleukin-2 and 5-FU has been associated with the highest reported response rates in non-randomised studies.^{9, 31} Furthermore, this triple regime has been compared with tamoxifen in one randomised trial. In this trial, 78 patients were randomised to triple therapy as described in the phase II studies or to eight weeks of tamoxifen therapy.¹⁰ There were substantial differences in response rates, 39% of triple therapy-treated patients responding, compared with none of the tamoxifen-treated patients. Median survival was improved from 14 months to over 42 months ($p < 0.04$). This has prompted two ongoing randomised trials to evaluate this triple regime in the adjuvant setting and in patients with metastatic disease, randomising this regime against single agent interferon (MRC/EORTC). Whether the reportedly higher response rates to this triple regime are owing to the drug combination *per se* is unclear. In a randomised trial, 131 patients were randomised to interleukin-2 and interferon or to the same and 5FU. No differences were detected in any study endpoint.²⁷ This emphasises the need to study the interferon- α , interleukin-2 and 5-FU regime in more detail. It is of interest that, although the same three drugs were used in both studies, there were marked differences in the schedule used.²⁷

Other schedules of cytokines or the additional use of agents such as 13-*cis*-retinoic acid do not appear to produce any additional benefits.²⁰ A phase II trial examined the effects of a therapeutic regime consisting of oral capecitabine, interferon- α 2a, interleukin-2 and 13-*cis*-retinoic acid in outpatients with metastatic renal cell cancer.³⁵ Complete and partial responses were achieved in 7% and 27%, respectively.

In a non-randomised study, out-patients were assigned interleukin-2 alone, interleukin-2 and 5-FU or interleukin-2 and 5-FU and interferon.³⁴ Respective response rates were 6%, 28% and 39%, with corresponding median survivals of 4.8 months, 15 months and greater than 32 months. The addition of 5-FU appears to enhance the efficacy of this combination.

There is no evidence from a randomised trial that medroxyprogesterone acetate improves quality of life during treatment with vinblastine and interferon.³⁰

Conclusion

Interferon- α is currently the standard treatment for patients with metastatic renal cancer who are suitable for systemic anticancer therapy. The effectiveness of more complex regimes, such as interferon, interleukin-2 and 5-FU, is yet to be confirmed.

Table 9.1a: The role of adjuvant therapy in renal cancer : systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Motzer, 2000. ²⁰ USA III	To determine the efficacy of systemic therapy for patients with advanced renal cell carcinoma.	<p><i>Participants</i></p> <p>Adults with renal cell carcinoma.</p> <p><i>Interventions</i></p> <p>Chemotherapy agents, immunotherapy, combination programmes and adjuvant therapy.</p> <p><i>Design</i></p> <p>Phase II and Phase III clinical trials.</p>	<p>Response rates.</p> <p>Progression-free survival.</p> <p>Toxicity.</p>	<p>51 phase II trials were located.</p> <p><i>Chemotherapy and resistance modulation (n = 1,347 patients)</i></p> <p>Response rates for floxuridine ranged from 0% to 14%. The response rate for vinblastine alone or in combination with a drug-resistance modifier was 3%. No single agent produced response rates which would justify its use. Interferon-α and Interleukin-2 gave low response rates, ranging from 10% to 20%.</p> <p>Response-rates among patients treated with low dose interleukin-2 were similar to those achieved when the drug was administered according to its high-dose bolus schedule.</p> <p><i>Immunotherapy</i></p> <p>Studies investigating interferon enrolled a total of 1,042 patients. The overall response rate ranged from 12% to 30%. Longer survival was associated with high performance status, prior nephrectomy and lung-predominant metastases. The duration of response rarely exceeded 2 years. A maximum dose of 5MIU to 20MIU of recombinant interferon-α daily avoids the toxicity of higher doses.</p> <p>The improvement in survival can be attributed to interferon-α, although quality of life issues need to be considered.</p> <p>Studies investigating interleukin-2 (IL2) found an overall response rate of 14%. The median duration of response was 23 months. A median survival of 16 months and a median duration of response of 54 months was seen.</p> <p>Combination protocols investigating interferon-α and vinblastine achieved a high response rate in several single-arm phase II trials but failed to show improved survival in 3 RCTs.</p> <p>In 23 trials (with a total of 607 patients), the combination of IL2 and interferon-α gave a 19% response rate. This rate was similar to response rate of IL2 alone.</p> <p><i>Surgery</i></p> <p>Nephrectomy as palliation and for improvement in quality of</p>	<p>Little information on methodology information and no search strategy or quality assessment criteria were given.</p> <p>Reviews a large amount of information on many phase two trials addressing systemic therapy.</p>	<p><i>Review question</i></p> <p>Yes</p> <p><i>Literature search</i></p> <p>MEDLINE and Cancerlit were searched from January 1990 to December 1998. No search strategy was provided.</p> <p><i>Inclusion criteria</i></p> <p>Phase II and phase III clinical trials where results of systemic therapy are included.</p> <p><i>Quality assessment</i></p> <p>None provided.</p> <p><i>Study details</i></p> <p>Yes</p> <p><i>Appropriate synthesis of results</i></p> <p>No formal meta-analysis.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
				<p>life may be justified. Rarely, nephrectomy is associated with spontaneous regression of distant metastases (< 1% incidence).</p> <p>Surgical resection of solitary metastases in selected patients resulted in a 5 year survival rate of about 30%.</p> <p><i>Adjuvant therapy after nephrectomy</i> RCTs showed no support for post nephrectomy radiotherapy.</p> <p>No evidence of benefit for adjuvant IFN-α after complete resection was seen in terms of recurrence-free and overall survival.</p>		

Table 9.1b: The role of adjuvant therapy in renal cancer: primary studies

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Figlin, 1999. ⁸ USA II	To compare low-dose IL2 alone with IL2 and CD8 ⁺ tumour infiltrating lymphocytes (TIL) in metastatic renal cell carcinoma.	<p><i>Participants</i> Patients aged at least 18 years with metastatic renal cell carcinoma and having a resectable primary tumour.</p> <p><i>Interventions</i> All patients underwent nephrectomy and then received rIL2 on days 1 to 4 of each treatment week at a dose of 5MIU/m².</p> <p>Patients were randomised to receive placebo infusion or an infusion of CD8⁺ TIL isolated and expanded from the nephrectomy specimen.</p> <p><i>Design</i> RCT.</p>	<p>Complete remission.</p> <p>Disease progression.</p> <p>Overall survival.</p> <p>Dose-limiting toxicity.</p>	<p>160 patients were recruited from 29 centres. 79 patients were randomised to be treated with IL2 alone while 81 patients were randomised to the combination therapy group.</p> <p>39 of the 81 patients who were randomised to receive tumour infiltrating lymphocytes (TIL) received the treatment owing to insufficient TIL yield from the nephrectomy tissue.</p> <p>Analysis was by intention to treat.</p> <p><i>Efficacy</i> 9 of 79 patients (11.4%) who were randomised to receive IL2 therapy alone and 8 of 81 patients (9.9%) who were randomised to combination therapy (logistic regression, $p = 0.75$).</p> <p>The median survival among patients treated with IL2 alone was 11.5 months as compared with 12.8 months for patients treated with the combination therapy ($p = 0.55$).</p> <p>After analysis of data from 80 patients the trial was terminated owing to a lack of efficacy.</p>	<p>This multicentre study does not confirm the benefit of CD8⁺ TIL infusion with low-dose recombinant IL2.</p> <p>However, the low rate of actual administration of TILs (48%) was markedly lower than in the pilot study (96%) in which TILs were shown to be effective.</p> <p>Administration of TILs may be difficult in the routine setting.</p>	<p><i>Randomisation</i> Yes</p> <p>Patients were randomised to receive a placebo infusion or an infusion of CD8⁺ lymphocytes (TIL) isolated and expanded from the nephrectomy specimen.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Intention to treat analysis was used.</p> <p>Logistic regression was used in the analysis of patients responding to treatment.</p> <p>χ^2 statistics were used Fischer's exact test used to compare the proportion of responders between the two treatment groups.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Galligioni, 1996. ⁶ Italy II	To investigate the effect of adjuvant active specific immunotherapy (ASI) in patients with non-metastatic renal carcinoma.	<p><i>Participants</i> Patients with TNM Stage I to III renal cell carcinoma with a surgically resectable primary tumour and an Eastern Co-operative Oncology Group performance status 0 to 1, who had undergone nephrectomy.</p> <p><i>Interventions</i> Patients were randomised to receive ASI or to a control group. ASI comprised of vaccination using bacillus Calmette-Guerin (BCG) and irradiated autologous tumour cells (IATC). Patients randomised to receive ASI received a weekly intradermal injection of 10⁷ viable BCG organisms and 10⁷ IATC in the first two weeks. The BCG was omitted in the third week. Patients in the control arm received no vaccination.</p> <p><i>Design</i> RCT.</p>	<p>Disease-free survival (DFS).</p> <p>Overall survival (OS).</p> <p>Evidence of delayed-type cutaneous hypersensitivity (DTCH).</p>	<p>120 patients were randomised in the trial; 76 males and 44 females joined the study. Each arm contained 60.</p> <p><i>Efficacy</i> Median follow-up of 61 months, 25 patients (20.8%) treated with immunotherapy and 20 patients (16.7%) from the control group had relapsed. 63% of patients treated with immunotherapy were alive at five years with no evidence of disease. This compares with 72% of patients who were randomised to the control group. The difference was not, however, significant ($p = 0.21$). 69% of patients treated with immunotherapy were alive at five years. This compares with 78% of patients who were randomised to the control group. The difference was not, however, significant ($p = 0.28$). In treated patients there was no significant relationship between disease-free survival or overall survival and the intensity of the DTCH response.</p> <p><i>Toxicity</i> All patients had baseline DTCH tests. Responses were negative in all patients. Patients in the immunotherapy arm showed increased responses at one month (70.4%, significant, $p < 0.01$), six months (56.8%) and 12 months (57.1%). The DTCH response remained negative in all control patients. No systemic toxicity was observed. Local ulceration attributed to BCG occurred at the intradermal injection site of the first two injections with healing in about 2 months.</p>	<p>ASI appears to increase the DTCH reactivity to autologous tumour but has no significant effect on disease-free survival or overall survival in patients with renal cell carcinoma.</p>	<p><i>Randomisation</i> Yes. Patients were randomised in equal numbers to either a treatment or control group.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Kaplan Meier and Wilcoxon test were used to calculate significance. Students t test was also used.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Pizzocaro, 2001. ⁷ USA II	To compare adjuvant recombinant interferon- α 2b (rIFN- α 2b) with observation after radical nephrectomy.	<p><i>Participants</i> Patients with pathological Robson stages II and III renal cell carcinoma (T3a, N0, M0 and T3b, N0, M0, or T2/3, N1to 3, M0) treated by radical nephrectomy.</p> <p><i>Interventions</i> Adjuvant rIFN-α2b compared with observation after radical nephrectomy. Adjuvant rIFN-α2b was administered 3 times per week for 6 months starting within one month of surgery.</p> <p><i>Design</i> RCT.</p>	Overall survival. Event-free survival. Time to death. Relapse rate. Toxicity.	<p>264 patients were randomised and, of these, 247 were assessable. 123 patients were randomised to the interferon therapy and 124 patients were randomised to observation.</p> <p>No advantage was demonstrated for adjuvant interferon therapy over observation in terms of overall and event-free survival (95% CI: 0.67 to 1.61, $p = 0.86$), with the possible exception of patients with pN2 to pN3 patients.</p> <p>51 of 123 patients (41%) randomised to interferon therapy and 38 of 124 patients (31%) randomised to observation had relapsed after a median follow-up of 62 months (range 5 months to 99 months).</p> <p>37 of 123 patients (30%) randomised to interferon therapy and 33 of 124 patients (27%) randomised to observation had died as a direct result of their disease.</p> <p>There was no significant difference in the rate of event-free survival between the two groups (HR 1.41, 95% CI: 0.93 to 2.15, $p = 0.11$). Whilst the treatment did not affect the overall event-free survival, a highly significant interaction between treatment and pN category was demonstrated ($p = 0.0001$). When compared with observation, rIFN-α2b had a harmful effect in patients with stage pN0 disease (HR 2.2; 95% CI 1.3 to 3.9, $n = 97$) and a protective effect in stage pN2 to pN3 disease (HR 0.19; 95% CI 0.06 to 0.63, $n = 13$).</p> <p><i>Toxicity</i> Toxicity was observed in 68 of 123 patients (55.3%) of patients given rIFN-α2b; 43 of 123 patients (35%) developing flu like symptoms. There were signs of hepatic (2 of 123 patients, 1.6%) and haematological (4 of 123 patients, 3.3%) toxicity while 19 of 123 patients (15.4%) developed a combination of the three.</p>	Alternative staging system used.	<p><i>Randomisation</i> Yes.</p> <p><i>Allocation concealment</i> Stratification was according to a scheme of balanced randomised blocks of eight patients each.</p> <p><i>Completeness of patient data</i> Yes.</p> <p><i>Appropriate analysis of results</i> The Kaplan Meier method, Cox's multiple regression models, the Gail and Simon test and univariate and multivariate analysis were used.</p>



Table 9.2: Metastatic renal cancer – interferon-alpha based immunotherapy with or without radical nephrectomy: RCTs

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Flanigan, 2000. ¹⁵ USA II	To evaluate the effect of nephrectomy prior to interferon treatment in patients with metastatic renal cancer.	<p><i>Participants</i> Patients with operable metastatic renal cancer.</p> <p><i>Intervention</i> All patients received interferon 5MIU/m² three days per week until progression. In one arm patients received radical nephrectomy prior to interferon.</p> <p><i>Design</i> Randomised trial.</p>	Survival.	<p>246 patients were randomised, 123 per arm; of these three were ineligible. The median follow-up was 187 days.</p> <p><i>Efficacy</i> The median survival time in the non-nephrectomy group was 8.1 months and in the nephrectomy group 12.5 months (p = 0.033).</p>	<p>This study provides evidence that nephrectomy prior to systemic therapy yields a survival benefit.</p> <p>This study is available only as an abstract.</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>
Mickisch, 2000. ¹⁶ The Netherlands, Russia, Belgium II	To compare interferon-based immunotherapy alone with immunotherapy and radical nephrectomy in metastatic renal cell carcinoma.	<p><i>Participants</i> Patients with histologically confirmed metastatic renal cell carcinoma and a respectable primary tumour.</p> <p><i>Interventions</i> Nephrectomy and, if possible, lymphadenectomy.</p> <p>Interferon-α 5 x 10⁶FFIU/m² three times per week for 52 weeks or until progression or unacceptable side-effects. Treatment was commenced within 1 month of surgery.</p> <p><i>Design</i> RCT</p>	<p>Disease progression.</p> <p>Complete or partial response.</p> <p>Survival.</p>	<p>88 patients were randomised (of which 2 were ineligible), 42 to surgery and immunotherapy and 43 to immunotherapy alone.</p> <p>The proportion of patients experiencing complete or partial response, stable disease or progression did not differ significantly between treatment arms (p = 0.38).</p> <p>Nephrectomised patients had an increased median time to progression (HR 0.60, 95%CI 0.36 to 0.97, p = 0.04) and an increased median survival time (HR 0.54, 95% CI 0.31 to 0.94, p = 0.03).</p>	<p>The authors conclude that radical nephrectomy before interferon-based therapy might delay progression and improve survival of patients with metastatic disease.</p>	<p><i>Randomisation</i> Yes.</p> <p><i>Allocation concealment</i> No</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes</p>

Table 9.3a: Cytokines, alone or in combination, in the management of renal cancer: systematic reviews

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Coppin, 2000. ¹⁸ USA I	To compare immunotherapy (IL2 and IFN- α) with non-immunotherapy in patients with metastatic or locally advanced renal cell carcinoma.	<p><i>Participants</i> Patients with metastatic or locally advanced renal cell carcinoma.</p> <p><i>Interventions</i> High-dose IL2 and IFN-α.</p> <p><i>Design</i> RCTs having immunotherapy in at least one arm.</p>	Survival. Response rate. Toxicity.	<p>42 RCTs involving 4,216 patients were located. All 42 studies reported response rates and 26 studies (3,089 patients) reported survival outcome.</p> <p><i>Efficacy</i> The average response rate over all treatments in the 42 studies was 10.2 % (range 0% to 39%). Complete responses were seen in 123 of 3,852 patients (3.2%, 38 studies, not reported in 4 studies). The median survival time was 11.6 months; The one-year survival rate was 48% and the two-year survival rate was 22%. No correlation was found between the response rate and the median survival time or between the response rate and the one-year survival rate. In 6 studies (963 patients) IFN-α significantly reduced the odds ratio for death at one year (OR 0.67; 95% CI: 0.50 to 0.89). A pooled hazard ratio for survival of 0.78 (95% CI: 0.67 to 0.90) suggests a significant treatment effect at 24 months from randomisation resulting in an average increase in the median survival time of 2.6 months. Enhancement of immunotherapy by increased dosage and the addition of combinations of agents to IL2 or IFN-α failed to improve survival.¹⁸ While IFN-α has shown a modest survival benefit compared with commonly-used treatments, IL2 alone has not been evaluated in RCTs. Evaluation of study quality is hampered by inadequate descriptions in the published reports and the small size of the majority of trials.</p> <p><i>Toxicity</i> Dose reduction owing to toxicity was required in an average of 31% of patients in studies reporting survival. An influenza-like syndrome was reported in the majority of patients.</p>	<p>A well structured and detailed systematic review.</p> <p>Studies on IL2 and survival compared with no cytokine not available.</p> <p>Further information on patient toxicity and quality of life may have added to the analysis.</p>	<p><i>Review question</i> Yes</p> <p><i>Literature search</i> MEDLINE, Cancerlit EMBASE and The Cochrane Controlled Trials Register were searched from 1999. International Meetings Abstracts of the AUA and ECCO were hand searched from 1996 to 1999.</p> <p><i>Inclusion criteria</i> RCTs were considered eligible if they included an immuno-therapeutic component in at least one trial arm and considered overall survival or response to treatment among patients with metastatic or locally advanced inoperable renal cell carcinoma.</p> <p><i>Quality assessment</i> The reviewers reported that a lack of detail in the primary reports prevented their adequately assessing the quality of included studies.</p> <p><i>Study details</i> Yes. Data extraction was performed by two independent reviewers.</p> <p><i>Appropriate synthesis of results</i> Dichotomous outcomes for treatment response and for deaths at one year were used as the main comparisons. Survival hazard ratios were used for studies of interferon-α against controls.</p>

Study Country Grade	Aims	Included studies	Outcomes	Results	Comments	Methods
Hernberg, 1999. ¹⁹ Finland I	To compare the efficacy of regimens with or without interferon- α in metastatic renal cell carcinoma.	<p><i>Participants</i> Adults with advanced renal cell carcinoma.</p> <p><i>Interventions</i> Regimens with and without IFN-α.</p> <p><i>Design</i> RCTs in metastatic renal cell cancer having no IFN-α in at least one arm.</p>	WHO or ECOG objective response criteria. Survival.	<p>The review found 8 trials (total n = 525). Of these, 6 studies have been published and 2 studies were unpublished.</p> <p>40 of 288 patients (14%) who had been randomised to receive IFN experienced a response. 19 of 237 patients (8%) who had been randomised to the control group experienced a response.</p> <p>From a meta-analysis of the odds ratios of the 8 studies, the pooled odds ratio was calculated at 0.47 (p = 0.013) and supported a benefit to patients treated with IFN.</p> <p><i>One year survival</i> Pooled OR = 0.46 in favour of IFN (n = 266, 3 studies, 95%CI 0.28 to 0.75).</p>		<p><i>Review question</i> Yes</p> <p><i>Literature search</i> A search was made of MEDLINE and the databases held at the NCI, Schering-Plough and Hoffman-la Roche to February 1997. No search strategy was provided.</p> <p><i>Inclusion criteria</i> RCTs with no IFN in at least one arm and adequate reporting of the number of events.</p> <p><i>Quality assessment</i> Not stated</p> <p><i>Study details</i> Yes</p> <p><i>Appropriate synthesis of results</i> Yes</p>

Table 9.3b: Cytokines, alone or in combination, in the management of renal cancer: RCTs

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Atzpodien, 1997. ¹⁰ Germany II	To compare oral tamoxifen with a combination of IL2, IFN and 5-FU in patients with metastatic renal cell carcinoma.	<p><i>Participants</i> Patients with progressive metastatic renal cell carcinoma.</p> <p><i>Interventions</i> Oral tamoxifen was administered at a dose of 45mg/m² twice daily on weeks 1 to 8. Subcutaneous IL2 was administered at a dose of 10MIU/m² twice daily on days 3 to 5 of weeks 1 and 4 and a dose of 5MIU/m² on days 1, 3 and 5 of weeks 2 and 3. Subcutaneous IFN was administered at a dose of 6MIU/m² on day 1 of weeks 1 and 4 and days 1, 3 and 5 of weeks 2 and 3 and at a dose of 9MIU/m² on days 1, 3 and 5 of weeks 5 to 8. An intravenous bolus of 5-FU 1,000mg/m² once weekly during weeks 5 to 8. Treatment was given on an outpatient basis.</p> <p><i>Design</i> RCT.</p>	Partial and complete response. Progression-free survival. Overall survival.	<p>38 patients were randomised to tamoxifen and 41 to the combination of IL2, IFN and 5-FU.</p> <p><i>Efficacy</i> There were no objective responses among the 37 evaluable patients who were randomised to receive tamoxifen. Of the 41 patients who were randomised to combination therapy, 7 patients had a complete response and 9 patients had a partial response. This gave an overall response rate of 16 patients in 41 (39%, 95% CI: 24% to 55%). The median time to progression was 4 months for patients randomised to tamoxifen and 13 months for patients who were randomised to receive combination therapy (p < 0.01). The median overall survival was 14 months for patients who had been randomised to tamoxifen as compared with more than 42 months for patients treated with IL2, IFN and 5-FU (p < 0.04).</p>	This study appears to be published in abstract form only.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Very little methodological information since only a short abstract. Patients randomised to two arms and were well balanced in terms of demographic characteristics.</p>
Boccardo, 1998. ²⁸ Italy II	To compare interleukin-2 alone, interferon alone and IL2 and IFN in advanced RCC.	<p><i>Participants</i> Patients with histologically proven advanced RCC aged 75 or less.</p> <p><i>Interventions</i> Patients were randomised to receive IL2 alone, IFN alone or IL2 and IFN in combination. Recombinant IL2 was administered at a dose of 18 x 10⁶ IU/m², 4 days</p>	Partial and complete response. Time to disease progression. Drug-related toxicity.	<p>66 patients were enrolled from 5 institutions. 22 patients were randomised to each arm and 55 were evaluable.</p> <p><i>Efficacy</i> 2 of 22 patients (9.1%) randomised to receive IL2 therapy achieved a complete response. This compared with no complete response among patients randomised to receive IFN therapy and one complete response (4.5%) seen in patients randomised to the combination regime. 3 of 22 patients (13.6%) randomised to receive IL2 therapy achieved a</p>	The numbers of responders is very low so differences should be treated with caution.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of</i></p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
		<p>repeated 8 times.</p> <p>IFN was administered at a dose of 6×10^6 IU/m² 3 days per week for 52 weeks.</p> <p>Patients randomised to the combined therapy had the drugs administered as above; rIL2 was given for 6 cycles. rIFN was then given weekly over 24 weeks.</p> <p><i>Design</i> RCT.</p>		<p>partial response. This compared with 2 of 22 patients (9%) among patients randomised to receive IFN therapy and one partial response (4.5%) seen in patients randomised to the combination regime.</p> <p>The median duration of response to IL2 was 18 months (range 9.5 months to 24 months). The duration of the two responses achieved with IFN alone was 7 and 9 months.</p> <p>In a logistic regression model restricted to patients receiving rIL2, the most powerful predictor of response was the total rIL2 dose ($p = 0.04$).</p> <p><i>Toxicity</i> Virtually all patients had some toxicity but only a minority had grade 3 to 4. There was a greater range of grade 3 to 4 toxicities among patients treated with IL2 than was seen in patients treated with IFN. With IL2 one third of patients developed severe hypotension.</p>		<p><i>results</i> Yes, given the small numbers of responses.</p>
Gleave, 1998. ²⁹ Canada. II	To compare interferon- γ 1b with placebo in patients with metastatic renal cell cancer.	<p><i>Participants</i> Patients with histologically confirmed metastatic renal cell carcinoma not curable by surgery. All patients had a life expectancy of at least 12 weeks and a Karnofsky performance score of at least 70.</p> <p><i>Interventions</i> All cases were treated by nephrectomy or angio-infarction at least three weeks before entry.</p> <p>Either recombinant human interferon-γ1b 60μg/m² or placebo self-administered subcutaneously once weekly.</p> <p><i>Design</i> RCT.</p>	<p>Complete or partial response.</p> <p>Disease progression.</p> <p>Overall survival.</p> <p>Toxicity.</p>	<p>197 patients were recruited from 17 centres in Canada. Ninety-eight were randomised to interferon and 99 to placebo of which 91 and 90 respectively were evaluable.</p> <p><i>Efficacy</i> The overall response rate among patients randomised to receive interferon was 4.4% and was 6.6% for patients randomised to receive the placebo preparation ($p = 0.54$).</p> <p>The median duration of response among patients randomised to receive interferon was greater than 11 months and was seven months for patients randomised to receive the placebo preparation ($p = 0.11$).</p> <p>The median time to progression among patients randomised to each group was 1.9 months, based on 181 patients (log-rank, $p = 0.49$).</p> <p>The median overall survival among patients randomised to receive interferon was 12.2 months and was 15.7 months for patients randomised to receive the placebo preparation (log rank, $p = 0.52$).</p> <p><i>Toxicity</i> 91% of patients randomised to receive interferon therapy experienced WHO Grade I toxicity and 61% experienced Grade II toxicities. 76% of patients randomised to the control arm experienced Grade I toxicity and 63% experienced Grade II toxicities.</p>	No differences in outcomes were observed in patients with renal cell carcinoma treated with interferon- γ 1b when compared with placebo.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Yes.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Jayson, 1998. ²¹ UK II	To compare interleukin-2 (IL2) alone with IL2 and interferon- α (IFN- α) in advanced renal cancer.	<p><i>Participants</i> Patients with progressive metastatic renal cancer. All had undergone previous nephrectomy for RCC.</p> <p><i>Interventions</i> All patients received IL2 (18 MIU Monday to Friday during 3 of every 4 weeks). Three cycles were administered.</p> <p>Patients were randomised to no further treatment or to IFN-α 9MIU (given Monday, Wednesday and Friday during 3 of every 4 weeks).</p> <p><i>Design</i> RCT.</p>	Complete response. Partial response. Disease progression.	<p>60 patients were enrolled in the study and 30 were randomised to each arm.</p> <p><i>Efficacy</i> No complete responses and only two partial responses were seen in the IL2 alone arm.</p> <p>Twelve patients in each group achieved stabilisation of disease.</p> <p>Progressive disease during therapy occurred in 51% of patients treated with IL2 alone and in 57% of the patients treated with both IL2 and IFN-α. There was no significant difference in the time to progression ($p = 0.18$).</p> <p>Median survival was 444 days for patients treated with IL2 alone 381 days for patients treated with the combination of IL2 and IFN ($p = 0.98$).</p> <p><i>Toxicity</i> The combination regime was associated with more fatigue and vomiting than was IL2 alone. In the single agent arm, 26 of 30 patients completed 2 cycles of therapy and 22 of 30 patients completed 3 cycles. In the combination therapy arm, fewer patients received their second cycle (25 of 30 patients) and third cycle (14 of 30 patients).</p>	<p>There was no evidence that the addition of IFN to IL2 increased the response rate while it did seem to increase toxicity.</p> <p>No evident statistical analysis of toxicity data.</p>	<p><i>Randomisation</i> Yes.</p> <p>Randomisation took place between 1993 and 1996 to one of two treatment arms.</p> <p><i>Allocation concealment</i> Not stated</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Toxicity data were not analysed statistically.</p> <p>Little information on methods of analysis was presented.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Medical Research Council Renal Cancer Collaborators, 1999. ²³ UK II	To compare interferon- α (IFN- α) with oral medroxy-progesterone acetate (MPA) in metastatic renal cancer.	<p><i>Participants</i> Patients with histologically or cytologically confirmed renal cell carcinoma with measurable metastatic disease. Some patients were nephrectomised.</p> <p><i>Interventions</i> Patients were randomised to receive IFN-α (10MIU by subcutaneous injection 3 times weekly for 12 weeks) or MPA (300mg orally each day for 12 weeks).</p> <p><i>Design</i> RCT.</p>	<p>Clinical response within 6 months.</p> <p>Progression-free survival.</p> <p>Survival.</p> <p>QoL.</p>	<p>335 patients were recruited from 31 centres. 167 patients were randomised to IFN and 168 patients were randomised to MPA.</p> <p>In the analysis patients were stratified according to nephrectomy status.</p> <p>Survival was improved in patients randomised to receive IFN therapy (HR 0.72, 95% CI: 0.55 to 0.93, $p = 0.017$). The median survival time was 2.5 months longer for patients randomised to receive IFN-α than for patients randomised to receive MPA.</p> <p>Patients who were treated with IFN were less like to die of progression than patients who were treated with MPA (HR 0.72, 95% CI: 0.56 to 0.92, $p = 0.009$).</p> <p>No significant interaction between treatment and any subgroup (e.g. nephrectomy) was detected.</p> <p><i>Quality of life</i> At 4 weeks nearly all side effects were significantly worse with IFN, but at 12 weeks the differences had decreased indicating possible adaptation to IFN.</p>	<p>Accrual stopped following the sixth analysis owing to evidence of effects on overall survival.</p> <p>Treatment with IFN should be considered in patients with metastatic renal cancer.</p>	<p><i>Randomisation</i> Yes.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes.</p> <p><i>Appropriate analysis of results</i> This trial was designed using a group sequential design (triangular test) and the estimated unbiased treatment effect.</p> <p>Logrank statistics were calculated.</p>
Motzer, 2000. ²⁴ USA II	To compare interferon- α 2a (IFN) alone with IFN and 13- <i>cis</i> -retinoic acid (CRA) in advanced renal cell cancer.	<p><i>Participants</i> Patients with advanced RCC. Patients with brain metastases were excluded.</p> <p><i>Interventions</i> IFN was administered subcutaneously daily and escalated to 9MIU unless grade 2 toxicity or above occurred, in which case escalation was stopped. Patients who were randomised to combination therapy were given CRA at a dose of 1mg/kg/day and IFN as above. Treatment was continued until the occurrence of disease progression, complete response or toxicity.</p> <p><i>Design</i></p>	<p>Complete or partial response.</p> <p>Survival.</p> <p>QoL.</p> <p>Trial Outcome Index (TOI) used as a summary measure of physical and functional well-being.</p> <p>QoL (FACT v3).</p>	<p>284 patients were randomised in the study. Of these 145 patients were randomised to receive IFN only and 139 patients were randomised to receive both IFN and CRA.</p> <p><i>Efficacy</i> Overall, 25 of 284 patients (9%) had a complete or partial response. There were 5 complete responses in the 139 patients (3.6%) being treated by the IFN and CRA combination. 11 patients (7.9%) in this group had a partial response. There was 1 complete response in the 145 patients (0.7%) being treated by the IFN and CRA combination. 8 patients (5.5%) in this group had a partial response. This difference in response rates between the groups was not statistically significant ($p = 0.14$). The median duration of response was 33 months in those patients treated with both IFN and CRA and was significantly superior to the response duration of 22 months seen in those patients treated with only IFN ($p = 0.03$). The overall median progression-free survival was 5 months with no significant difference between the arms ($p = 0.13$). At 24 months, 19% of patients given IFN and CRA were progression-</p>	<p>Response rates and survival were not improved by the addition of CRA to IFN.</p> <p>However, there was evidence for an increase in the duration of both response and progression-free survival attributable to CRA.</p> <p>Both treatments decreased</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
		RCT.		<p>free compared with 10% of patients given IFN alone ($p = 0.05$).</p> <p>There was no significant difference in survival between the two arms (overall median, 15 months, $p = 0.26$).</p> <p><i>Toxicity</i> No difference in toxicity was observed between the two arms.</p> <p>In both arms over 8 weeks there was a decrease in Quality of Life scores, which was significantly more pronounced in patients who received both IFN and CRA arm than in patients who received IFN alone ($p = 0.02$).</p>	QoL; this was especially true of the combination.	
Negrier, 2000. ²⁷ France II	To evaluate the addition of 5-fluorouracil (5-FU) to a combination treatment using rIL2 and rIFN- α 2a in metastatic renal cancer.	<p><i>Participants</i> Patients with histologically-confirmed metastatic renal cell carcinoma, aged 18 to 80 years and with an Eastern Co-operative Oncology Group performance score of < 1.</p> <p><i>Interventions</i> All patients received a combination of recombinant IL2 and recombinant IFN. They were randomised to receive 5-FU in addition or to receive no further treatment.</p> <p>rIL2 was administered sub-cutaneously at a dose of 9MIU per day, 6 days per week.</p> <p>rIFN was administered at a dose of 6MIU per day, 3 days per week.</p> <p>rIFN and rIL2 were given during weeks 1, 3, 5 and 7.</p> <p>5-FU was administered 5 days per week as a continuous infusion during weeks 1 and 5 at a dose of 600mg/m²/day.</p> <p><i>Design</i> RCT.</p>	<p>Response rate.</p> <p>Progression-free survival.</p> <p>Overall survival.</p> <p>Toxicity.</p>	<p>131 patients were recruited from 24 institutions and were randomised to receive IL2 and IFN (Arm A, n = 70) or IL2, IFN and 5-FU (Arm B, n = 61).</p> <p>Median follow-up was 23 months.</p> <p><i>Efficacy</i> No complete response was observed in either arm. There was one partial response in Arm A and five in Arm B. This trend was not significant ($p = 0.1$).</p> <p>12% of patients randomised to Arm A and 15% of patients randomised to Arm B had survived with progression-free disease at one year. No significant difference was demonstrated.</p> <p>Overall, 53% of patients randomised to Arm A and 52% of patients randomised to Arm B were alive one year following randomisation. Again, no significant difference was demonstrated.</p> <p><i>Toxicity</i> The most common side-effects were grade 3 or 4 impairment of general status or digestive disorders. No significant difference in toxicity was observed between the two arms and no toxicity-related death occurred.</p>	The trial closed prematurely owing to low overall response rate.	<p><i>Randomisation</i> Yes Eligible patients were randomised at the data monitoring centre by an interactive computerised procedure.</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes. Intention to treat analysis was used. Categorical variables were compared using the χ^2 test or Fischer's exact test. The Kaplan Meier and log rank methods were used.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Negrier, 1998. ²² France II	To determine the effect of interleukin-2 (IL2), interferon-alpha (IFN α) or both in metastatic renal cell cancer.	<p><i>Participants</i> Patients with metastatic renal cell cancer</p> <p><i>Interventions</i> Patients were randomised to receive recombinant human IL2 alone, (Group 1), IFNα alone (Group 2) or both (Group 3). IL2 was administered as a 5-day infusion at a dose of 18MIU/m²/day. The same dose of IL2 was given to patients in Group 1 and Group 3. IFNα was given subcutaneously at a dose of 18MIU/day three times a week for 10 weeks and then for an 13 additional weeks as maintenance to patients in Group 2. Patients in Group 3 were administered IFNα at a dose of 6MIU/day three times a week during the first two cycles of IL2 and each IL2 maintenance cycle.</p> <p><i>Design</i> Multicentre randomised trial.</p>	Response rate. Event-free survival (survival without progression). Overall survival.	<p>425 patients were randomised in the study; of these 138 patients were allocated to Group 1, 147 patients were allocated to Group 2 and 140 patients were allocated to Group 3.</p> <p>Induction treatment was given to 132 patients in Group 1, 146 patients in Group 2 and 136 patients in Group 3. 29 patients in Group 1, 59 patients in Group 2 and 47 patients in Group 3 received maintenance treatment. Median follow-up was 39 months.</p> <p><i>Efficacy</i> Response rates were 6.5% for patients in Group 1, 7.5% for patients in Group 2 and 18.6% for patients in Group 3 ($p < 0.01$). Event-free survival at 1 year were 15% for patients in Group 1, 12% for patients in Group 2 and 20% for patients in Group 3 ($p = 0.01$). The median survival times were 12 months for patients in Group 1, 13 months for patients in Group 2 and 17 months for patients in Group 3 ($p = 0.55$)</p> <p><i>Toxicity</i> More adverse events were seen in patients given IL2. The predominant effects were fever and hypotension.</p>	Need to balance increased response and longer event-free survival of combination cytokine therapy with increased toxicity.	<p><i>Randomisation</i> Yes. Stratified by centre.</p> <p><i>Allocation concealment</i> Interactive computer procedure.</p> <p><i>Completeness of patient data</i> Yes.</p> <p><i>Appropriate analysis of results</i> Survival curves were calculated by the Kaplan-Meier method and data were compared using the log-rank test.</p>
Pyrhonen, 1999. ²⁶ Finland II	To compare interferon (IFN) and vinblastine (VBL) compared with vinblastine alone.	<p><i>Participants</i> Patients having locally advanced or metastatic renal cell carcinoma, aged less than 75 years and with a life expectancy of more than 3 months.</p> <p><i>Interventions</i> Patients were randomised to receive IFN and VBL or VBL alone. Treatment continued for 12 months or until progression.</p>	Overall survival. Response rates. Duration of response. Time to progression.	<p>160 patients were recruited from 3 Finnish University Clinics. 79 patients were randomised to receive IFN and VBL while 81 patients were randomised to receive VBL alone.</p> <p><i>Efficacy</i> The overall response rate for patients who were treated with IFN and VBL was 16.5% while 2.5% of patients who were treated with VBL alone responded to therapy ($p = 0.0025$). The median overall survival of patients treated with IFN and VBL was 67.6 weeks while the patients treated with VBL alone was 37.8 weeks (log-rank, $p = 0.005$).</p>	The addition of VBL to IFN significantly improves response rate, overall survival and progression-free survival.	<p><i>Randomisation</i> Yes.</p> <p><i>Allocation concealment</i> Not stated</p> <p><i>Completeness of patient data</i> Yes. No patients lost to follow-up.</p> <p><i>Appropriate analysis of results</i></p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
		<p>or until progression.</p> <p>VBL was administered intravenously at a dose of 0.1mg/kg every three weeks.</p> <p>IFN was administered subcutaneously at 3MIU three times per week for 1 week and 18MIU three times per week for the remaining weeks. The dose was reduced to 9MIU in patients with low tolerance.</p> <p><i>Design</i> RCT.</p>		<p>The median progression-free survival was 13 weeks for patients treated with the combination of IFN and VLB while patients treated with VLB alone had a median progression free survival of 9 weeks (log-rank, p = 0.0001).</p>		<p>Yes.</p>
<p>Radosavljevic, 2000.³⁰ Yugoslavia II</p>	<p>To evaluate the addition of medroxy-progesterone acetate (MPA) on quality of life during treatment with vinblastine (VBL) and interferon (IFN).</p>	<p><i>Participants</i> Patients with advanced renal cell carcinoma.</p> <p><i>Interventions</i> All patients received vinblastine and interferon. Patients were randomised to receive medroxyprogesterone or no additional treatment.</p> <p>Overall 247 cycles were administered.</p> <p><i>Design</i> RCT.</p>	<p>QoL using the Rotterdam Symptom Checklist (1990 version).</p>	<p>81 patients were recruited to the study.</p> <p>During treatment the QoL score worsened in both arms. At no stage was there a significant difference in score between the two arms however.</p>	<p>There is no evidence that MPA improved the quality of life of patients during treatment with VBL and IFN in renal cell cancer.</p>	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Very little methodological information was given in the report – a short abstract. The arms were well balanced in terms of demographic characteristics.</p>

Study Country Grade	Aims	Study design	Outcomes	Results	Comments	Methods
Tsavaris, 2000. ²⁵ Greece II	To compare the toxicity of high-dose interferon (IFN) compared with low-dose interferon and vinblastine (VBL), over 12 weeks of treatment.	<p><i>Participants</i> Patients with metastatic renal cell carcinoma.</p> <p><i>Interventions</i> High-dose IFN consisted of 16MIU three times weekly. Low-dose IFN consisted of 5MIU three times weekly and was combined with 6mg/m² of VBL every 14 days.</p> <p><i>Design</i> RCT.</p>	Toxicity. Partial and complete response rates. Cost.	<p>100 consecutive patients were randomised to high-dose IFN or to low-dose IFN and VBL.</p> <p>11 of 50 patients (22%) randomised to IFN only, developed leucopenia. 22 patients (44%) who were treated with IFN and VBL developed leucopenia. The difference in the rate of leucopenia was statistically significant (0.013).</p> <p>24 of 50 patients (48%) of patients randomised to IFN only developed severe fatigue. 7 patients (14%) who were treated with IFN and VBL developed severe fatigue. The difference in the rate of leucopenia was statistically significant (0.0008).</p> <p>26 of 50 patients (52%) randomised to IFN only, developed weight loss of greater than 10% of their body weight 10 patients (20%) who were treated with IFN and VBL developed severe weight loss. The difference in the rate of severe weight loss was statistically significant ($p = 0.002$).</p> <p>The mean duration of fever was significantly longer in the high-dose IFN group than in the IFN with VBL group by a factor of 1.3 to 2.5 ($p < 0.001$).</p> <p>There was no significant difference between the arms in any response criterion. Overall, responses were identified in 18 of 100 patients (18%) and the duration of response was 4 to 64 weeks.</p> <p>The direct cost of the IFN and VBL regime was 39% that for high-dose IFN.</p>	When compared with high-dose IFN, the use of low-dose IFN with VBL: reduces toxicity (except leucopenia) but does not affect the response rate.	<p><i>Randomisation</i> Yes</p> <p><i>Allocation concealment</i> Not stated.</p> <p><i>Completeness of patient data</i> Yes</p> <p><i>Appropriate analysis of results</i> Yes.</p>

Table 9.3c: Cytokines, alone or in combination, in the management of renal cancer: non-randomised primary studies

Study Country Grade	Aims	Study design	Outcomes	Result	Comments	Methods
Lopez Hanninen, 1996. ³⁴ Germany VI	To estimate the efficacy and tolerance of home based interleukin-2 therapy in metastatic renal cell carcinoma.	<p><i>Participants</i> Patients with histologically-confirmed progressive metastatic renal cell carcinoma treated at a single institution.</p> <p><i>Interventions</i> Patients were allocated to one of three arms. Arm A consisted of Interleukin-2. Arm B consisted of Interleukin-2 and interferon-α2. Arm C consisted of interferon-2, interferon-α2 and 5-fluorouracil.</p> <p>Interleukin-2 was given at a dose of 5 to 20MIU/m².</p> <p>Interferon-α2 was given at a dose of 6MIU/m².</p> <p>5-fluorouracil was given at a dose of 750mg/m².</p> <p>Administration 1 to 10 times per week for up to 8 weeks.</p> <p><i>Design</i> Non-randomised study.</p>	Complete and partial response (WHO response criteria). Disease progression. Survival. Toxicity.	<p>215 consecutive patients were assigned to one of three risk groups according to known prognostic variables. 16 patients were allocated to the Arm A, 79 patients were allocated to Arm B and 120 patients were allocated to Arm C.</p> <p><i>Efficacy</i> 6% of patients allocated to Arm A, responded to therapy. This compared with a 28% response rate among patients allocated to Arm B and a 39% response rate among patients who were allocated to Arm C.</p> <p>Among those who had an intermediate risk, median survival was 4.8 months in patients allocated to Arm A, 15 months in patients allocated to Arm B and greater than 32 months in patients allocated to Arm C, ($p < 0.0001$).</p> <p><i>Toxicity</i> In most patients toxicity was limited to WHO grades 1 and 2, permitting outpatient management. Grade 3 toxicity was observed in 2% to 7% of cycles and required a 50% reduction in the doses of IL2 and IFN.</p>	<p>The authors comment that this outpatient-based therapy can be as effective as the most aggressive intravenous IL2 regime, but with reduced toxicity.</p> <p>Note that in this retrospective study patients were not randomised to the given regimes.</p> <p>An Editorial Comment points out that the response rate to IL2 alone is slightly lower than in selected previous studies but acknowledges that the addition of 5-FU appears to enhance efficacy.</p>	<p><i>Allocation to groups</i> Patients were allocated at the discretion of their physician, whose decision was based on the clinician's assessment of risk of relapse.</p> <p><i>Allocation concealment</i> Fail – professionals and patients were not blind to the allocation.</p> <p><i>Entry point</i> Pass</p> <p><i>Inclusion/exclusion criteria</i> Pass</p> <p><i>Comparability of groups</i> Pass</p> <p><i>Objectivity of outcomes assessment</i> Pass</p> <p><i>Point estimates/variance indicators for the primary endpoint</i> Pass</p> <p><i>Appropriate analysis</i> Pass</p>



Study Country Grade	Aims	Study design	Outcomes	Result	Comments	Methods
Jones, 1993. ³² UK VI	To compare the survival of patients with advanced renal cancer treated with interleukin-2 to that of matched patients taken from the Eastern Co-operative Oncology Group database.	<p><i>Participants</i> Patients with advanced adenocarcinoma of the kidney.</p> <p><i>Intervention</i> Treatment with recombinant interleukin-2.</p> <p><i>Design</i> Multivariate analysis comparing published survival data to that of a matched set of controls treated with chemotherapy from the ECOG database.</p>	Toxicity. Tumours response. Survival.	<p>327 evaluable patients in 5 multicentre studies were treated with continuous infusion rIL2. The survival of these patients was compared in a multivariate analysis to that of 390 patients receiving chemotherapy derived from the ECOG database.</p> <p><i>Efficacy</i> The overall response rate to IL2 was 14%. Median duration of remission was 357 days from partial remissions and greater than 926 days for complete remissions.</p> <p>The median survival for IL2-treated cases was 342 days and for the ECOG controls was 229 days ($p = 0.0001$). The survival benefit owing to IL2 was more pronounced in good prognosis patients.</p> <p><i>Toxicity</i> Five cases required admission to intensive care owing to toxicity and there were three deaths attributed to IL2.</p>	A well analysed study supporting the view that IL2 confers a survival advantage in advanced renal cancer. Prospective trials are required to test this hypothesis.	<p><i>Case definition</i> Pass</p> <p><i>Reliability of disease assessment</i> Pass</p> <p><i>Random selection of controls</i> Not stated</p> <p><i>Comparability of controls and participants</i> Pass</p> <p><i>Assessment of interventions</i> Pass</p> <p><i>Response definition</i> Pass</p> <p><i>Over-matching</i> Not stated</p> <p><i>Appropriateness of analysis</i> Pass</p>
Motzer, 2000. ³⁵ USA VI	To evaluate the benefit of cytokine therapy, chemotherapy and nephrectomy in patients with advanced renal cell carcinoma.	<p><i>Participants</i> Patients with advanced renal cell carcinoma treated in 24 clinical trials of therapy with nephrectomy, chemotherapeutic agents or cytokines.</p> <p><i>Interventions</i> Trials were of cytokine therapy (interferon-α, interleukin-2) or chemotherapy (cytotoxic or hormone therapy). Some patients in the trials had undergone nephrectomised.</p> <p><i>Design</i> Multivariate analysis of 24 trials.</p>	Overall survival.	<p>Data on 670 patients from 24 consecutive trials on cytokine or chemotherapeutic therapies.</p> <p>The median survival time for patients who had undergone cytokine therapy was 13 months ($n = 396$, 95% CI: 12 to 15). The median survival among patients treated with chemotherapy was 6 months ($n = 274$, 95% CI: 5 to 8; $p < 0.0001$). This conclusion was the same for trials conducted in the 1980's and the 1990's.</p> <p>Patients having had prior nephrectomy and a time from initial diagnosis to treatment of greater than 1 year had a significantly higher median survival time than other patients ($p = 0.001$).</p>	Patients were not randomised to the treatment regimes. This is a multivariate analysis based on 24 trials of systemic chemotherapy or cytokine therapy.	<p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> Pass</p>

Study Country Grade	Aims	Study design	Outcomes	Result	Comments	Methods
Oevermann, 2000. ³⁵ Germany. VI	Phase II trial to evaluate the effect of capecitabine-based home therapy that includes IFN- α 2a, IL2 and 13- <i>cis</i> -retinoic acid.	<p><i>Participants</i> Patients with metastatic renal cell carcinoma treated as outpatients.</p> <p><i>Interventions</i> Oral capecitabine at 1,000mg/m² twice daily on days 1 to 5 of weeks 5 to 8. 13-<i>cis</i>-retinoic acid at 34mg/m² daily during weeks 1 to 8. Interferon at 5MIU/m² per day on day 1 of weeks 5 to 8. Interleukin-2 at 10MIU/m² per day on days 3, 4 and 5 of weeks 1 and 4 and at 5MIU/m² on days 1, 3 and 5 of weeks 2 and 3.</p> <p><i>Design</i> Non-randomised study.</p>	Complete and partial remission. Disease progression. WHO graded toxicity.	<p>The median follow-up was 8 months. 30 patients were recruited to the study.</p> <p><i>Efficacy</i> 2 of 30 (6.7%) patients achieved a complete response. A further 8 of 30 patients (26.7%) achieved a partial response. 12 of 30 patients (40%) attained stable disease status. 8 of 30 patients (26.7%) experienced progressive disease. The duration of the responses ranged from 4 months to greater than 10 months. All responses except one were ongoing at the end of follow-up.</p> <p><i>Toxicity</i> No patients experienced WHO grade 4 toxicity. No toxic deaths occurred.</p>	This study concludes that the substitution of capecitabine for 5-FU does not reduce clinical efficacy although in this phase II trial no direct comparison between the two agents is available. Capecitabine was administered orally in the outpatient setting.	<p><i>Sample</i> Pass</p> <p><i>Inclusions</i> Pass</p> <p><i>Entry point</i> Pass</p> <p><i>Follow up</i> Pass</p> <p><i>Outcomes</i> Pass</p> <p><i>Sub series</i> N/A</p>

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Patients' Views of Urological Cancer Services and Developing National Guidance

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Introduction

The National Cancer Alliance (NCA) was commissioned to undertake a small-scale exercise to enable urological cancer patients to input their views, knowledge and experience into the development of the guidance.

Aim and objectives

The aim of the exercise was to input patient and carers' perspectives into the development of the national guidance on the management of urological cancers. To achieve this aim, the following objectives were set:

- To provide patient and carer perspectives about urological cancer services
- To provide patient and carer feedback on the national guidance proposals.

The agreed emphasis of the exercise was on patient perspectives and this was reflected in the recruitment.

Structure of report

The report is structured in the following way:

Methods	This section describes the research methods used, the conduct of the recruitment, how recruitment was conducted and gives the profile of the patient respondents recruited to the discussion group.
Results	Results are presented in three sections and give the main findings, structured around the main areas identified from the proposals, namely: raising awareness, investigations at the GP's surgery and speedy referral, diagnosis, treatment and after care. Respondent recommendations in each area are given at the end of each sections.
Patient Awareness	In this section responses to presenting symptoms are considered. Patients views on raising awareness are discussed.
GP investigations/referral	This section details the patients' experiences of investigations carried out by the GP. Referral to the hospital is discussed.
Hospital assessment/diagnosis	This section explores patients' experiences of investigations in the hospital setting and of receiving a diagnosis of cancer.
Treatment and after care	This section details findings relating to treatment choices. Treatment and care are discussed. Specific consideration is given in this section to patient information and support issues. Brief mention is also made of issues relating to follow-up/after care.
Conclusions	This section draws together some overall implications of the research.

Methods

As explained in the introduction, the broad aim of the project was to obtain patient and carer views of the proposed guidance, through eliciting an in-depth response from patients who recently or currently were in receipt of urological cancer services.

Qualitative research methods lend themselves to this aim and so, for this reason, a discussion group methodology was chosen. This allowed a group of respondents to meet together in an informal environment under the direction of a moderator. Using a discussion brief, areas identified in the proposals were discussed rather than specific questions asked. This flexibility allows issues considered salient to the members of the group to be explored in-depth. Full details of the discussion brief and the format of the interview may be obtained from the NHS Centre for Reviews and Dissemination, University of York.

In order to augment the findings from the discussion group and to facilitate patients unable to attend to contribute, written submissions were also accepted.

Recruitment

The majority of the recruitment to the focus group took place between July and September 2000. A variety of recruitment methods were used and included sending publicity information to urology Cancer Nurse Specialists, Cancer Information Centres, support groups, cancer charities and National Cancer Alliance (NCA) contacts. In addition, press releases were sent to local radio stations and local newspapers throughout England. Using these methods, people who had had a diagnosis of any of the urological cancers were invited to participate in a discussion group and asked to contact the NCA if interested. The project consultant then contacted each of the respondents to tell them about the project and establish their eligibility to participate in the discussion group. A standard recruitment form was used to confirm eligibility. All respondents were advised that participation in the discussion groups was voluntary and their contributions would be anonymised. Details of the profile of the patients are given below.

Prior to attending the discussion group all respondents received a letter of invitation and a summary of the key recommendations in the proposals prepared by the NCA. This summary was provided because the proposals comprised some 22 discrete proposals written with varying degrees of accessibility. Respondents were still, however, offered copies of the full set of the proposals or those that were specific to their cancer. All those respondents who made written submissions received a copy of the NCA summary and all the proposals.

When reference is made in the report to respondents who made a written submission, this is clearly indicated, otherwise, all references to respondents refer to those that participated in the discussion group.

Discussion group

The discussion group took place at the King's Fund in London and was facilitated by Becky Miles, Director of the NCA and Catherine Smith, Project

Consultant. The discussion was tape-recorded for transcribing with the permission of the respondents.

Profile of respondents

Using the recruitment methods described above, 11 respondents were recruited to the discussion group and, on the day, ten were able to attend - nine patient respondents and one carer respondent. Numbers were restricted in order to ensure an in-depth discussion.

The age range of the respondents in the discussion group was from 32 to 77 years, seven were male and three female, one of whom was a carer. Respondents were from the following areas: Berkshire, Hertfordshire, London, Merseyside, Middlesex, Norfolk, Surrey, Sussex and Warwickshire.

Summary profile of patients who participated in the discussion group						
How they heard about the discussion group	Publicity via support group network	Local newspapers	Local radio	NCA Contacts	Cancer Information Centres	Cancer Charities
	4	1	1	2	1	1
Year of diagnosis	1993	1994	1996	1997	1998	1999
	1	1	2	2	1	2
Cancer diagnosed	Bladder		Prostate		Kidney	
	1		5 (2 with metastases)		3 (all with metastases)	

In addition, seven written submissions were received from six patients with prostate cancer and one patient with bladder cancer. These submissions were from the following areas: Cardiff, Kent, Hertfordshire, Merseyside, Middlesex, Surrey, West Midlands.

Patient awareness and responses to 'early' symptoms

With the aim of earlier diagnosis, the urological guidance places emphasis on 'raising awareness' among patients, GPs and their staff and the general population, regarding the 'cardinal symptoms' for urological cancers.

'Cardinal symptoms' for urological cancers

Microscopic/Frank blood in the urine (especially if painless).
 Microscopic blood in the urine in adults over 50 years.
 Symptoms of chronic cystitis without proof of infection.
 Solid lump in the body of the testis
 Possible loin mass.
 Warty/ulcerated/bleeding lesion on the glans penis.
 Possible symptom clusters involving bone pain, outflow obstruction and non-specific features of malignant disease such as weight loss or general malaise.

A1

This section considers respondents' experience of symptoms and their views about 'raising awareness' of urological cancers in the general population and among patients.

General population and patients

All respondents (those in the discussion group and those who gave written submissions) were in agreement that early diagnosis of cancer was of paramount importance. They believed, therefore, that, 'raising awareness' about the early warning signs or symptoms of possible urological cancers, was very important. The common view was that there was a correlation between early diagnosis and subsequent improved prognosis.

However, frequent reference was made by nearly all respondents regarding the difficulty of detecting urological cancers and patients being seemingly asymptomatic or presenting with 'non-specific' symptoms. Examples given of 'non-specific' symptoms included: high blood pressure, headaches and unusual sweating and these were not recognised, either by themselves or later by their GPs as possible symptoms of their cancer:

"One of the problems with kidney cancer is that it doesn't present very specific symptoms until you perhaps lose blood or identify a physical lump or have loin pain."

(Kidney cancer patient)

Despite this, respondents identified a particular need for awareness to be raised among men, especially regarding prostate cancer, of likely symptoms and the need to take early action:

"You are your own best guardian sometimes, aren't you."

(Kidney cancer patient)

Some of the prostate cancer respondents had the symptom of needing to pass water frequently at night but described contrasting responses to having this symptom. One respondent said he simply put it down to growing older whereas another, even when friends and subsequently the GP, also put the symptoms as "being down to his age", continued to be concerned.

A few respondents commented on the reluctance, in the general population and among some health professionals, to talk openly about cancer. One respondent said that in the African-Caribbean community, cancer continues to be known as the "Big C".

Patients' recommendations

On the basis of their experience, respondents recommended that the following should be reflected in or directly incorporated into the urological guidance:

- For the general public to become more aware of the key symptoms of urological cancers using targeted publicity campaigns, information and leaflets.

- It was felt especially important that men be encouraged to become more aware of their health and to take early action if symptoms present.
- It was suggested that Well-Men clinics are held and that men should be actively encouraged to attend regularly.
- Targeting women who were partners or related to men in higher risk groups, to help encourage them to seek medical attention was also thought to be potentially helpful.
- In relation to men and women, there was a broad suggestion for a regular health check to be undertaken by the GP (or other primary care team member), akin to going for regular dental check-ups. However, the resource implications were recognised and it was felt a health-check could be aimed at higher risk groups. (The rationale behind this was linked to keeping a car roadworthy, with a regular MOT.)
- It was recommended that there should be a health education programme aimed at informing the public on what prostate cancer is and what tests are available for its early detection. Raising awareness by the use of television and radio advertisements, ad-shells and posters in public lavatories, in pubs or in clubs was strongly advocated.
- A need was identified for the widespread promotion of help line telephone numbers of support associations and other organisations providing a help and information service. Respondents advised that free booklets should be displayed prominently in libraries, surgeries, clinics and other public places.

Investigations at the general practice and referral

The guidance discusses the need to undertake initial investigations and, if appropriate, for a speedy referral to be made by the GP to the hospital. The intention is to ensure that patients have both speedier diagnosis and access to treatment. As well, the guidance refers to the need for patients to have information at each stage, with the rationale that this will make patients more likely to go to hospital and have treatment.

GP variation in practice

Many respondents spoke of the need for GPs to '*know the whole person*' and to take a holistic approach when assessing their patients' health. Some commented on the brevity of consultations and GPs looking at the computer screen rather than their patient and the difficulty of then establishing a rapport.

Several respondents reported seeing different GPs at their practice with the same symptoms. Of note was the GP variation, within and between practices, in interpretation of symptoms and consequent action. GP responses and respondent views of those responses are considered in more detail below.

At one end of the spectrum were two respondents who described attending the GP with a health problem, apparently unrelated to their subsequent diagnosis of a urological cancer and the GP, through asking routine general health questions,

deciding to undertake routine tests and/or physical examinations which then led to a prompt referral to a specialist. At the other end of the spectrum were several respondents who described continuing to return to the GP with non-specific symptoms because they knew something was not right. It should be emphasised at this point that respondents agreed it must be difficult for GPs to know how to respond to patients who present with non-specific symptoms.

‘Cardinal’ symptoms

The findings from this very small-scale study suggested that there may be a need for GPs’ awareness to continue to be raised about the ‘cardinal symptoms’ for urological cancers.

Three respondents related having prompt referrals following a GP consultation. One described going to the GP with a general concern that *‘things were not quite right down below’* and the GP immediately referred the respondent to the hospital for a series of scans. Two other respondents presented to their GP with prominent lumps (one on the side and one in the neck), that had appeared suddenly and were discovered by chance. These symptoms were immediately recognised by the GP as requiring speedy referral for further investigation.

Three other respondents, one in a written submission, related presenting their GP with symptoms which could be indicative of a urological cancer but that, initially, their symptoms were not recognised of being of consequence. The onus in each case was on the respondent returning to the GP either to encourage them to investigate the symptoms or, if initial investigation had taken place, to encourage the GP to make a referral. One respondent, who was subsequently diagnosed as having bladder cancer, presented to the GP on three occasions with painless haematuria:

*“I had to take the initiative to go back to my GP and say
look it still hasn’t cleared up, still got the blood.”*
(Bladder cancer patient)

This respondent related how persistence and querying the GP’s proposal to repeat a urine test when no evidence of infection was shown in the first test led to the GP deciding to make a referral to hospital.

The remaining two respondents, both of whom had subsequent diagnoses of prostate cancer, described returning to the GP on several occasions prior to referral. One, in his 70’s, explained that his symptoms were put down by two different GPs in his practice as ‘being due to his age’. It was not until the third visit a year later, when he had an appointment with his usual GP that he underwent a DRE and PSA test which then led to a referral. In a written submission, the other respondent described attending his GP for over a year before a hospital referral was made. During this time the GP had advised that his PSA readings, while raised, were not high enough for referral. This respondent advised that following his diagnosis, the GP has since changed their practice and would now make an earlier referral.

Asymptomatic or non-specific symptoms

The issue of being completely asymptomatic, for prostate and kidney patients or presenting with non-specific, multiple symptoms over a prolonged period of

time was debated by the group in some detail. It was also recognised that some patients were apparently asymptomatic until their cancer had already advanced to a late stage.

Two respondents described continually returning to the GP with a range of non-specific symptoms, one over a four year period, which were not recognised as having a possible link with the presence of a urological cancer and then having a dramatic onset of a 'cardinal symptom' which resulted in a direct admission to hospital via accident and emergency.

For those patients who repeatedly presented to their GPs with non-specific symptoms, it was proposed that there should be a clearly staged and well-managed diagnostic process within a set time scale. If findings remain inconclusive, additional tests and investigations or referral for a specialist opinion should follow.

Speedy referral

For clarity, it is re-iterated that this is a small-scale qualitative study which does not claim to be representative of all urological cancer patients. Nonetheless, in this sample, the elapsed time before being referred by the GP for specialist investigation ranged from a matter of days to well over four years. This may suggest that the proposal in the guidance for elapsed time before referral by the GP to be used as a performance measure would be of real value.

Several respondents felt it would be a good idea for GPs to follow nationally agreed referral guidelines, unaware that these have recently been developed and published by the Department of Health. On learning of the existence of such guidelines, there was interest in their status and how adherence was monitored. The introduction of referral guidelines was welcomed by the group.

In analysing the transcript from the discussion group and the written submissions, it appeared that having one or a combination of the following 'assets' were able to get speedier access to specialist services:

- private health insurance
- a good deal of knowledge
- access to others (professionals or other cancer patients) with knowledge and experience of the NHS
- strong self-advocacy skills

"One thing the GP asked me straightaway was do you have health insurance? and he said it will speed things up. And I was seen within 3 to 4 days."

(Kidney cancer patient)

Information for patients

All respondents described a lack of information at the GP surgery and many said that receiving written information from the GP or it simply being available within the surgery would have been helpful:

“So I had a letter from the oncology department, a word which I had never heard, so I went ...looked up the dictionary, ‘ the investigation of tumours, particularly cancerous.’”

(Prostate cancer patient)

Patients’ recommendations

On the basis of their experiences, respondents recommended that the following should be reflected in or incorporated into the urological guidance:

Referral guidelines, clinical practice and organisational issues

- GP referral guidelines should be disseminated widely and GP adherence closely monitored.
- For prostate cancer, GPs need explicit and consistent national guidance on what constitutes a ‘raised’ or ‘abnormal’ PSA level and when it appears with other presenting symptoms, if relevant, should trigger a first referral.
- To ensure a systematic approach, when GPs start investigations they need to draw them to a ‘conclusion’ and if GP investigations are inconclusive, to then ensure that the patient is referred for specialist investigation. (This applies to all symptoms whether ‘cardinal’ or non-specific.)
- Once patients are referred to hospital for specialist investigation, the GP should maintain an active interest in their patient from diagnosis and treatment(s) through to discharge and follow-up to ensure patients are not ‘lost in’ or ‘abandoned by’ the system.
- Having made the decision to make a referral, the process should be speeded up by GPs using standard referral forms and sending these directly to the relevant consultant or hospital department by fax or e-mail.

Hospital-based assessment and diagnosis

This section discusses findings relating to the assessment of patients in the hospital setting, to when they were given their diagnosis of cancer and their response to the guidance relating to diagnosis and assessment. The guidance proposals advocate the need for there to be a speedy, systematic and streamlined approach to assessment and diagnosis. The guidance repeatedly emphasises the role of multidisciplinary teams in the assessment and diagnosis of urological malignancies.

Assessment

The time taken from the first appointment at the hospital to the point of diagnosis, the ‘work-up’, varied from within 24 hours to over three months.

The fastest assessments took place for two respondents who had been admitted via accident and emergency and another who had private health insurance and received a prompt appointment for investigations. One respondent, having undergone some tests, ascertained from the radiographer that there was a possibility of her having cancer, but that to make a definitive diagnosis required

further investigation which the consultant advised could take two to three weeks. At this point the respondent explained that she had said to the consultant:

“You’ve just told me I may have cancer, you expect me to walk around for the next two or three weeks waiting for another test?”

(Bladder cancer patient)

As a result of this prompting and great concern expressed, the consultant made some enquiries and the further tests were undertaken within a week.

Communication and information

A few respondents described the period of having tests as being well-handled by their health professionals despite it being an increasingly anxious time. Having the reasons for the tests and what they would entail explained clearly seemed to help a good deal.

Many respondents referred to repeated visits to hospital(s) for different tests and several said that communication and information, to the patient or the GP, about what was happening and what would happen next was limited or almost non-existent:

“I went back ... had the urogram, didn’t have any more communication from my GP or from the hospital. The next thing I know is that I got a letter asking me to go for a camera in the bladder, but with no explanation as to why. So then I went for the cystoscopy...that was almost six weeks later, but I thought that was quite reasonable at that stage obviously.”

(Bladder cancer patient)

All respondents welcomed the proposal in the guidance for a speedy, systematic and streamlined approach to assessment and diagnosis. However, one respondent, in a written submission, expressed doubt regarding the viability and appropriateness of a ‘one-stop’ clinic for prostate cancer patients, specifically citing the lead-in times required for biopsies.

Receiving a diagnosis of cancer

It was apparent in the discussion group that their preparedness for a diagnosis of cancer varied greatly. This could be attributed to a number of factors which influenced their expectations and preparation for a diagnosis of cancer. Firstly, the nature of the symptoms and the respondents’ own level of awareness of cancer appeared to be an influence. The various responses of different health professionals and the information imparted prior to a definitive diagnosis also strongly influenced respondents. For example, one respondent, in a written submission, although concerned that his symptoms could indicate cancer, had had his concerns allayed by the response of health professionals and the consequent delays to him undergoing a full assessment. In this instance, when a diagnosis of cancer was made, it was, by this point, quite unexpected. Another respondent realised late in the assessment process that cancer was a possibility when there was mention of an oncology nurse:

“She [the nurse] said ‘I’ve arranged for the oncology nurse to come and speak to you’. As soon as she said oncology I knew that it meant business. You know they actually meant they thought I had cancer.”

(Bladder cancer patient)

For many respondents the diagnosis of cancer was not expected, despite undergoing extensive tests.

Where and how the diagnosis is communicated

The moment when patients are told they have cancer is often recalled vividly. The discussion group and all the written submissions highlighted how their diagnoses of cancer were given and whether information and support was available and readily offered. For all patients, how this point was handled was of the utmost importance. It was also apparent that for some how the diagnosis was told appeared to have a significant impact on their subsequent relationship with health professionals.

Most respondents were on their own when they received their diagnosis of cancer. Although prompted by the moderator, none recalled being advised to attend the consultation with someone. Most respondents, in the discussion group and the written submissions, were told their diagnosis of cancer by a consultant urologist. Respondents were told of their diagnosis of cancer in a range of different locations, nearly all within the hospital setting and with varying degrees of privacy. Several respondents also commented that there seemed to be a reluctance among some health professionals to use the word cancer which, in some instances, seemed to add to the confusion about what was the diagnosis. Beyond these factors, respondents described a quite disparate range of experiences, some positive, some negative and some both positive and negative.

A few examples were given of consultants imparting the diagnosis well. They found it helpful that the word cancer had been used directly, that information and support was offered and made available from nurses, who were present and that written literature was readily given:

“The day I went to get my diagnosis, apart from the consultant... there was also an oncology nurse who was then assigned to me to answer any questions or queries I had about everything.”

(Bladder cancer patient)

One respondent described being given the diagnosis in an initially hesitant but then very brusque way by a junior doctor whom she had never met before. She described how difficult he found it to impart the diagnosis, that he was unable to use the word cancer and she was left without explanation about the diagnosis, which was completely unexpected or what was to happen next:

"He just said you've got a malignant tumour on your right kidney and it's going to have to come out. Got up, walked out of the room. I thought he had gone out to get more results and he's coming back – He didn't come back."

(Kidney cancer patient)

One respondent related that his unexpected diagnosis was told to him while he was having lunch on a ward, in front of a group of doctors, other patients and staff on the ward and whoever else was passing by. This lack of privacy heightened his distress and engendered a feeling that he was not being treated with respect and dignity. Another, in a written submission, described attending a consultation, which lasted 15 minutes, alone and receiving an unexpected diagnosis which was interrupted by the consultant taking a call on a mobile telephone.

Another described being given the diagnosis by a consultant oncologist and there being no further information, either verbal or written, available for the respondent to understand, consider and/or reflect on the potential implications of the diagnosis:

"And everything was absolutely super except at the point at which I was told I had prostate cancer by the consultant whom I have an enormously high regard for ... the one thing that I think was lacking was that there was nothing to give me or tell me at the time of diagnosis so I then ... looked up everything I could find on prostate cancer because I did not know anyone in the world who had ever had it."

(Prostate cancer patient)

All respondents agreed that information and support, be it verbal and/or written and tailored to the needs of the individual, needs to be readily available at the time of diagnosis. A few respondents had received information and support from a clinical nurse specialist and felt this was a valuable role. Respondents who were kidney cancer patients drew attention to the paucity of patient literature available on kidney cancer.

The multidisciplinary team

Most respondents were unaware that they were being assessed by a 'team' of health professionals or for some, where there was some evidence of a team, there was little evidence of team working. The exception to this cited by a few respondents was where a consultant urologist worked closely with a specialist nurse and this approach was welcomed. It should be pointed out that all respondents were very aware of how busy their health professionals were and frequent references were made to how busy staff were, workload pressures and staff shortages.

Most respondents had not had access to a non-surgical oncologist at the point of diagnosis. This was raised by some in the group who had later seen a non-surgical oncologist and deemed this to be important. Two respondents thought that, in their experience, there was friction between oncology and surgical colleagues which had hindered their access to oncologists.

Patients' recommendations

On the basis of their experience, respondents recommended that the following should be reflected in or incorporated into the urological guidance:

Assessment

- Once the need for specialist investigation is decided, the patient and GP need to be kept fully informed of the process.
- The overall time scale for completing an assessment should be as rapid as possible and closely monitored by the hospital.

Giving a diagnosis of cancer

- It should be suggested that patients bring a relative or friend to the 'results' consultation and the patient, if unaccompanied, should not be left alone once the diagnosis is given unless they ask to be.
- Health professionals need to have very good communication skills to impart a diagnosis of cancer. It should be done by a senior and experienced member of staff and not left to junior doctors. The diagnosis and its implications needs to be fully explained, unless patients do not wish this and time needs to be given to patients to understand and assimilate the diagnosis.
- A trained and experienced clinical nurse specialist should be present at the diagnosis consultation and able to provide information and emotional support tailored to the needs of the individual.
- Written information, ideally talked through by health professionals, should be freely available and offered.
- Information about help lines, information and support centres, support groups and patient to patient support should be readily available.

Treatment and after care

The guidance proposals recommend planned and co-ordinated treatment provided by a team of trained staff, with equipment and facilities, who have weekly team meetings, who keep patients' notes and treatment plans which are also sent to the GP and, if appropriate, the patient.

It should be emphasised that the group was at pains to give praise where it was due or acknowledge the difficulties health professionals face, throughout the discussion. However, this section reflects the importance for patients of multidisciplinary team working and information and support which were absent or limited for many. The consequences of this was the focus of much criticism. This was particularly true when it led to a lack of a systematic process to ascertain their full diagnosis and determine the appropriate course of treatment.

Deciding treatment

Having received a diagnosis of cancer, all respondents stressed how important it was to understand the treatment options and their implications. From their perspective, this meant deciding treatment needed to be based not only on treatment effectiveness, but also side effects and quality of life issues. This was, therefore, a time when they wanted to be able to consider possible options,

read relevant patient literature and then ask their health professionals questions before determining the preferred option. Taking this approach seemed to be important to respondents in order that they could regain some control of what was happening to them, adjust to having a diagnosis of cancer and, through understanding, feel safer with any preferred treatment option.

In addition, there was a strong view within the group that the extent of diagnostic investigation needed to 'fit' with the treatment(s) available. As one respondent commented:

"The diagnosis is only as good as the treatments available under the National Health...The diagnosis must go as far as possible to determine which is the preference."

(Prostate cancer patient)

The importance of this was also described by a respondent in a written submission who discovered that further diagnostic investigations were required to determine whether his preferred course of treatment was the most appropriate. These further investigations were refused by his local hospital although he later found them to be standard practice elsewhere. He stressed that to undergo these further investigations was important to him on both a physical and psychological level:

"It was very important to me to know that I knew everything I could about my current medical situation and that I was on the best course. It would be difficult to handle if at a later time I learnt that I had chosen the wrong course of treatment."

(Prostate cancer patient)

Multidisciplinary team working

Several respondents spoke highly and some very highly, of their consultants – either those that they had been referred to or had sought out for themselves – and, where they were available, their clinical nurse specialists. Where problems arose for some, however, these related to having limited or no multidisciplinary team working.

"The consultant said he could not advise me as to which option would be best for me. As a surgeon he would choose surgery but if I asked an oncologist he would probably choose radiotherapy, each according to their own specialist interest".

(Prostate cancer patient)

When discussing treatment decisions, the issues of the importance of multidisciplinary team working again came to the fore. As discussed in the section of this document pertaining to the role of the multidisciplinary team in the assessment and diagnosis of malignancies, many respondents said they did not have the impression that their consultant was working as part of a team of other medical professionals.

Several respondents described being recommended a proposed course of treatment apparently on the basis of the judgement of only one health

professional, usually a consultant urologist, rather than it being described as the recommendation of the multidisciplinary team. The issue of not having the early contact with non-surgical oncologists, was raised by those who had later had access to this speciality. Concern was expressed by a few respondents about the lack of consultant oncologists in the NHS. One respondent described the two-fold impact this has as being firstly their lack of availability to patients and secondly, their limited professional knowledge of some urological cancers owing to the lack of sub-specialisation:

“...A typical oncologist deals with more than one form of cancer so this is an important issue. My oncologist, and its not his fault, does not have time to do all the research which I have done”.

(Kidney cancer patient)

Having the input of all relevant medical specialities was seen as especially important when having to understand and make complex and difficult treatment decisions, when the evidence was uncertain and opinions from different professionals varied. Respondents described how difficult it was to decide treatment options in these circumstances.

Another issue raised by several in the group and in a few of the written submissions related to instances where respondents had dealt with registrars who were unable to answer their questions about treatment. This raised the point, made strongly by the group and repeated, that it was important for medical professionals to acknowledge the boundaries of their own knowledge and to work within a multidisciplinary team in order to benefit from its collective knowledge, skills and experience.

A comparison was drawn regarding teamwork by the carer respondent who happened to have a diagnosis of breast cancer, between her husband's unfavourable and her own very favourable experience of team working at the same hospital. There was general agreement in the group that if breast cancer teams could work well then so could and should other cancer teams.

Discussion then ensued regarding how much, within and beyond the hospital, health professionals made optimum use of the available knowledge on particular cancers and their treatments within their team, locality, region and nationally.

Related to this, the importance of being informed about clinical trials was raised expressly by two respondents, who were themselves now being treated under trial protocols. In addition, international treatment and outcome comparisons were raised both in the context of multidisciplinary team working and in terms of the consistency of clinical decision-making and using the most up-to-date treatments.

Patient information and support

“I found the total lack of information is the thing that worried me more than having the cancer...and the battle to try and get answers from people.”

(Prostate cancer patient)

Another key issue which came to the fore during the discussion on deciding which treatments were appropriate was adequate information and support. Some consultants were clear in advising what they thought was the preferred option, others were not so clear and in a number of cases advised that the decision rested with the patient. Several who found themselves in this latter situation said that there was either no or very little information, verbal or written, available to help them make such an important decision.

A few respondents described being presented with a preferred treatment option by a consultant urologist and being comfortable at the time with the option proposed and so proceeding on that basis. For two of these respondents, retrospectively, the treatment agreed was still felt to be the best course of action. However, another who was presented with a particular treatment option as the most effective option, later discovered this not to be the case and moreover, that the treatment undergone had been experimental although he was not advised of this at the time. He commented:

“My point...is that if I'd had these alternatives set out in a written document I would have studied them and gone back to him next time with a list of questions”.

(Prostate cancer patient)

Other respondents felt that the treatment proposed had been satisfactory but a lack of information, verbal and written, had left them bewildered and fearful. The contrasting good and bad experiences of respondents are illustrated in the quotes below:

“...the specialist told me straightaway what I'd got, what they suggested I had done and I had pamphlets given to me, all about radiotherapy, the whole lot. And three booklets...”.

(Prostate cancer patient)

“When the results of the test came up, I was not told anything, I was not given any choice of treatment, I was livid with that particular hospital. The treatment I have, I have no complaints about, it's perfectly effective”.

(Prostate cancer patient)

One respondent described, in response to her request, her hospital facilitating contact with other patients who had had undergone the treatment being proposed. The respondent said this contact had been extremely valuable to her in accepting the proposed course of treatment and fully understanding its implications.

Two respondents described, one in a written submission, how following their diagnosis they had felt so bewildered by the conflicting professional opinions and lack of supporting information provided that they had undertaken their own research to determine the best treatment option. Both of these respondents described the value of considering other patients' case histories, taking advice from cancer help and support organisations and using the internet. One patient, in a written submission, explained that this approach had been triggered by his consultant urologist who, having given scant information, advised that it was for him, the patient, to determine what treatment option he should pursue. As a

result of their own research, both respondents had chosen a course of treatment (brachytherapy) which was not available to them locally and had not been presented as a treatment option to them by their health professionals.

What was striking was that for some, the onus had been placed on them, as patients, to take direct responsibility for determining their best treatment option. Moreover, this was without having any professional knowledge base or receiving supporting information to make that decision from their health professionals.

Where such instances arose it appeared that this occurred as a direct response to being in a vacuum where professional inputs were scarce, limited or lacking coherence rather than it being an initial, personal choice to approach their situation this way. Although many respondents welcomed being involved in the decision making process to determine the best course of treatment, they also wanted and needed to be supported in this process. To be left with direct and seemingly sole responsibility for deciding treatment was considered a stressful burden.

Undergoing treatment

There was limited discussion of respondent experiences of undergoing treatment. The main emphasis related to the importance of treatments being managed in a patient-centred way. For example, for some, timing treatment to fit in with their lives was important. The carer respondent described how important it was to her to stay with her husband throughout his stay in hospital for treatment. This was not supported or facilitated by hospital staff which for the carer and her husband undergoing treatment, added to the worry and stress of that time. Another respondent knew that help would be needed with her children when she was undergoing chemotherapy. After pressing the hospital on how help might be secured, she discovered that support was available via social services; it was only her persistence, borne of concern for the care of her very young children, that gleaned this information and then enabled her to secure this service and support:

“...it had to be me taking the initiative. Whereas really, they should have been thinking ahead, what support I would have needed”.

(Bladder cancer patient)

Several respondents stressed the importance and value of having a named health professional contact whom they could telephone or see during treatment with queries, problems or support. Many had no such contact.

Side effects

Short-term side effects of treatments seemed to have been communicated to most respondents. However, the chronic nature and severity of some, particularly later, side effects was not always communicated or, when they happened, managed effectively.

A key example of this was prostate cancer respondents who had experienced varying degrees of incontinence for which they were ill prepared and all unsupported. Again, only through lengthy research had some respondents

discovered what advice and support was available and these respondents in the discussion group immediately began to exchange information and contacts:

“It turned out that I was 100% incontinent after this operation...nobody at any stage offered me any help. My GP didn't say well we have a continence advisor in the area... The hospital didn't do anything at all... Most of all I've discovered, I've found out myself with the help of various charities, about the continence foundation.”

(Prostate cancer patient)

One respondent, who had participated in two clinical trials, said he had not been advised of the longer term severe side effects he was now having or told that such side effects were a possibility.

Follow-up care

There was limited mention of follow-up care by the group. Comments were, however, made on the need for co-ordinated care and consistent practice:

“It's just co-ordinating everything like, ... they don't seem to have a co-ordination between me having the test before I go for the consultation...I end up having the test after and having to go back ... to get the result which...is a total waste of time”.

(Bladder cancer patient)

“I would like there to be a plan. My main operation was five years ago, following that I had a bone scan which happily was clear. When I saw my consultant again (this year) I said isn't it time I had this checked again to see if there is any chance that it's spread and he said no. Now I don't know whether that is normal or whether the patient should be able to have it explained to him, what procedures there are to check that the cancer hasn't spread somewhere else”.

(Prostate cancer patient)

Palliative care

There were five members of the group who had metastases (including to the lungs and spine), two of whom said they had already survived well past their prognosis. The word palliative care was not used or raised by the group.

However, there was a keen concern among many of the group to know what was going to happen next to them, both in terms of their disease progression and the likely or possible symptoms they might experience. They also wanted to know what services, information and support would or could be available. In particular they wanted advice and support on how to prepare themselves for whatever was facing them in the future. Respondents did not expect health professionals to predict the future, but, on the basis of their professional experience and the stage of their cancer, wanted health professionals to be able to give them likely scenarios at the very least:

“What I want to know... is what’s going to happen. ... will I get breathless, will I be not able to walk? Will I end up in a wheelchair because it’s spread to my bones? What will happen to me?... I would like someone to sit down in my home and talk to me.”

(Kidney cancer patient)

“Well I know where I am now, but what happens later on? How much later on? What will I be able to do? How will my quality of life be changed? Are there any steps I could take now?”

(Prostate cancer patient)

The dialogue below, illustrates respondents trying to make sense for themselves why information and services were often not readily available to them. The penultimate quote also illustrates the difficulty of the onus for seeking out information and services resting with patients - how do patients know what they should ask and who they should ask, if they have no prior experience:

1. *“Is it because you don’t ask that these things don’t happen”.*
(Bladder cancer patient)
2. *“I’m sure that’s the answer”.*
(Prostate cancer patient)
3. *“The facilities are probably there, are they? Is it because people aren’t up front and don’t ask?”*
(Bladder cancer patient)
4. *“Where’s this list of things you can ask for?”*
(Prostate cancer patient)
5. *“Is it a case of doctors don’t say because people don’t ask and they don’t want to frighten people? Is that what it’s about?”*
(Bladder cancer patient)

Patients’ recommendations

On the basis of their experience, respondents recommended that the following should be reflected in or incorporated into the urological guidance:

- Regardless of where you live, the most effective and up-to-date treatments, including those on clinical trial, should be offered and made available.
- Treatment choices should be based on the recommendations of a team of medical experts, not just the opinion of one specialist or speciality.
- Treatment options and choices should be based on and informed by full and thorough diagnostic and staging information.
- Treatment options should be clearly presented to patients, the evidence base for those options clearly stated and written information on the options and evidence supporting those options should be readily available and always offered.

- Known side effects of proposed treatment options (short and longer term) should be given to patients in a considered way. (If side effects of a treatment are unknown but considered likely, this should be stated clearly.)
- Monitoring of side effects should take place and, where present, should be actively managed.
- Trained and experienced clinical nurse specialists or similar, should be available to provide information and support, including psycho-social support, when deciding treatment, throughout periods of treatment and after care.
- Patient to patient contact should be offered and facilitated by the hospital, so that people can be in touch with others who have undergone a similar treatment.
- Technology should be used to ensure that doctors have speedy and easy access to nationally accredited and regularly updated information on cancers, available treatments and clinical practice.
- Patient information should include a summary of how the clinics and doctors function together, their various responsibilities, a written explanation of the appointment system and who a patient can contact if necessary.
- Establishing a national infra-structure to co-ordinate effort on focused research to improve and develop the evidence base. (This infra-structure should take account of research from around the world.)

Conclusions

This section draws together overall conclusions. Specific patient recommendations on the urological guidance are given at the end of each of the previous sections and give a clear and wide-ranging steer.

Firstly, what was striking and salutary about undertaking this exercise was how willing and keen patients were to share their experience of urological cancer services. This was demonstrated by those who attended the group, many travelling some distance to do so, those who wished to attend but were unable to because of the restriction on numbers and those unable to attend but wanting to contribute by sending a written submission. The driving reasons for this was a strong desire to help improve health services for other patients and a real concern and willingness to directly help other patients through their own knowledge and experience.

Respondents reflected in a measured and considered way about the services they had received – the strengths, the weaknesses, but also the opportunities there were to make improvements, which would benefit both patients and professionals. In addition, many referred to the potential value of good and appropriate patient-patient support. This wealth of in-depth knowledge and experience, shared by those who participated, demonstrated the very real benefit to the NHS of finding ways to develop patient-centred services by learning directly from patient and carer experience. This rich source of

'intelligence' for the health services leads to the conclusion that it should be integrated directly into the planning and development of health services.

An underlying theme which was present throughout the discussion and in the written submissions was the need for both professional and patient knowledge, experience, skills to be networked and managed. This should be done at a local, regional, national and international level in order to make optimum use of existing resources. Many respondents had resorted to doing this on an individual basis in quite different and often painstaking ways and on a range of issues in order to try and avail themselves of the services that they needed. (For some this was starkly related to where inputs from the multidisciplinary team were scarce, limited or lacking coherence.)

In final conclusion, if the overall aim of the urological guidance is for commissioners to provide patient-centred, efficient and effective services, it will need to not only address the detailed 'content' of the service, but to also focus as much on the structures, systems and professionals needed to deliver the service, together with the linkages between them. This will help ensure that the content of the service remains appropriate and its delivery is successful.

Analysis of the Potential Economic Impact of Guidance on the Management of Urological Cancers

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Summary

The cost implications of the urological cancer guidance can be divided into five main categories, listed below. Three are general categories of relevance to all urological cancers, while the last two are site-specific.

- Multidisciplinary teams
- Centralisation
- Specialist nurses
- Prostate cancer (incidence and other costs)
- Bladder cancer (diagnostic testing and treatment)

The increase in costs for the diagnosis and treatment of patients with kidney, testicular and penile cancers is likely to be small.

Multidisciplinary teams

Multidisciplinary team (MDT) working is intended to ensure that patients benefit from the expertise of a range of specialists for their diagnosis and treatment, and that care is given according to recognised guidelines. For some cancers MDTs are well established in most trusts, but for urological cancers even the concept of MDTs is not well-accepted in all trusts.

While most centres hold regular MDT meetings, many have insufficient time to review all patients. At units the problems are more severe, with lack of administrative support being a particular problem. Both units and centres struggle to get a full team together, with the lack of availability of radiologists, pathologists and oncologists a special problem, exacerbated at units where they may only have visiting clinicians for a session every two weeks. The cost of ensuring that all MDTs have a co-ordinator, and of additional staff time for MDT meetings is estimated to be an additional £6.4 million per year.

Centralisation

The guidance recommends some centralisation of services, in particular requiring that MDTs which undertake radical prostatectomy and cystectomy should perform a combined total of at least 50 operations per year. Ideally there should be only one team per network, covering a population of at least one million people, undertaking this type of surgery. Analysis of the data shows that this is a radical change from current practice.

To estimate the effect of greater specialisation of services for radical prostatectomy and cystectomy, an analysis was undertaken of the current (1999/2000) number of operations by hospital, network and region, and an estimate made of the proportion of work that will have to move from units to centres in each network in order to fulfil the requirements of the guidance. Different configurations are possible, so maximum and minimum scenarios were developed to cover the likely range. The central cost estimate is £4.4 million per year, with a range of £3.8 to £5.0 million.

The impact on trusts taking on the work may be significant. Typically the number of prostatectomies and cystectomies they will undertake will more than double (from around 35 per year) as a result of the guidance, but increasing incidence of prostate cancer and more aggressive treatment of bladder cancer may also considerably increase the demand for these operations. This may mean that they have to increase their capacity by a factor of four or five, with knock-on effects on demand for theatre capacity and special care nursing.

Specialist nurses

The guidance emphasises the need for improved information and support for urological cancer patients, and the central role that nurse specialists should play in delivering more patient-centred care.

The current provision of nurse specialists is patchy. There are several specialist nurses who are providing the levels of support indicated in the guidance. However, some are stretched very thinly, being solely responsible for several hundred cancer patients. Audit data from the North West region suggests that many urological cancer patients do not receive counselling from a specialist nurse, and that consequently they may lack significant information about their treatment. The recent Commission for Health Improvement and Audit Commission (CHI/AC) report¹ indicates that at the time of the survey (winter 2000/2001) only around 50% of trusts providing a urological cancer service had a nurse specialist. The situation is changing rapidly with nurses being appointed, so for the cost estimate it is assumed that it is only 30% of trusts that still require a specialist nurse. For the 70% of trusts that are assumed to already have at least one nurse it will be assumed that on average they need 30% more nursing resources, on the basis that around 30% of specialist urological cancer nurses reported severe time constraints on the service that they could provide.¹

On the basis of these assumptions, around 80 more nurse specialists will be required, at an annual cost of £2.7 million. If it is assumed that these additional nurses will need to complete a post-registration diploma in oncology nursing (ENB 237) the training cost is £0.3 million.

Prostate cancer

Incidence

The greatest increase in the costs of caring for urological cancer patients over the next few years is likely to arise from the increasing incidence in prostate cancer, rather than in implementing the guidance. This probable increase in incidence is expected as a consequence of many more men being screened for prostate cancer with the PSA test. Many urologists believe that it is not just plausible, but probable, that incidence rates in the UK will rise to American levels. Whether incidence will really more than double, and how fast incidence will increase, is very difficult to predict. Currently there is very little hard evidence of an increase in incidence, but the latest national figures are for 1998. The 1998 figures do show an increase of 12.6% over 1997, which may signal the start of an upward trend, but could be owing to statistical variation.²⁻⁴ However, there is evidence that PSA testing increased during the late 1990s, and is likely to have increased further. Urologists report seeing many more patients with possible prostate cancer, and expect to see even more in the future.

Given this uncertainty, three different scenarios were devised. The highest increase assumes that there has been a steady increase from 1998 to 2001, but that incidence will then rise more steeply to reach American levels by 2004. This would give an incidence of 45,000 for England and Wales, compared to approximately 20,500 in 1998. The low scenario is based on a continuing steady increase from 1998 to 2004, with the central scenario based on mid-point estimates for 2001 and 2004. These scenarios give a range of additional costs of £15.4 to £43.8 million per year, with a central estimate of £28.2 million.

Other costs

The guidance will result in more patients having an MRI prior to radical treatment - not currently routine practice for all patients. This is likely to cost an additional £0.4 million. This cost should be more than offset by the reduction in bone scans. Scans are rarely useful for patients with a PSA level of less than 10ng/ml and Gleason score less than eight, but audit data suggests that a third of patients with localised cancer having a scan fall into this category. The potential annual cost saving is £0.5 million.

The guidance encourages the use of conformal radiotherapy where possible. Conformal radiotherapy requires more consultant oncologist, radiographer and medical physicist time than external beam radiotherapy. Assuming that machines are provided, the ongoing additional cost of providing all patients with conformal radiotherapy is modest, at £0.2 million per year. This total annual cost assumes cost savings resulting from the phasing out of the use of the low melting point alloy method of providing conformal radiotherapy, which is more laborious, and therefore more expensive, than conformal radiotherapy with multileaf collimators.

Bladder cancer

Audit and HES data show that patients are being more actively treated for bladder cancer than a few years ago, but that there is still a need for further improvement. Increased treatment costs will be incurred as a result of the guidance. Additional intravesical chemotherapy for superficial cancers will cost £2.4 million, and an additional 850 cystectomies a year may be required, at a cost of £3.9 million

Cost Summary

(All costs in millions of pounds per year)

Multidisciplinary teams

MDT co-ordinator for all units and additional consultant sessions	£3.56
Additional costs of staff time at units and centres	£2.84
Subtotal	£6.40

Centralisation- central **£4.39**

Low scenario	£3.79
High scenario	£4.98

Patient-centred care (specialist nurses) **£2.68**

Prostate cancer

Potential increase in prostate cancer incidence **£28.19**

Low scenario	£15.40
High scenario	£43.84

MRI prior to radical treatment **£0.37**

Low scenario	£0.23
High scenario	£0.40

Conformal radiotherapy for radical treatment **£0.16**

Low scenario	£0.10
High scenario	£0.17

Bone scans **-£0.53**

Low scenario	-£0.34
High scenario	-£0.58

Bladder cancer

Diagnosis	£0.28
Treatment	£5.93
Subtotal	£6.21

Total **£47.87**

Range **£34.47-£64.10**

1. Introduction

Guidance has been developed for the optimal organisation of service provision for urological cancers. Before commissioners and trusts can implement this guidance they need to assess the resource and cost implications. The School of Health and Related Research at the University of Sheffield (SchARR) has been commissioned to support the process by analysing the potential cost implications of the recommendations for urological cancers.

1.1 Scope

The objective of this economic analysis is to:

1. Identify how the guidance may affect commissioners and different types of service providers (e.g. local cancer units, specialist centres) in terms of changes in patient flows and services that need to be provided;
2. Identify different possible models of implementation, which will vary depending both on the baseline position and on the chosen means of achieving the targets set out in the guidance;
3. Identify the key economic issues and cost drivers of guidance implementation;
4. Estimate the costs of implementing the guidance according to the different models identified, and in so doing provide a structure and methodology that trusts may use for their own analysis;
5. Estimate the national cost implications of adopting the cancer guidance;
6. Illustrate how the national total additional cost will be phased with time according to possible scenarios for the introduction of the guidance.

The analysis does not aim to:

- give a definitive answer as to the cost implications of the guidance for specific cancer centres or units (but to produce an indication of the scale of costs involved for different paradigms);
- address in detail the training and workforce implications of the draft guidance;
- analyse the health outcome measures of meeting the draft guidance;
- estimate the cost-effectiveness of guidance implementation.

2. Process and methods

2.1 Integration of economic review with the cancer guidance

The research on cost implications was developed in parallel with the production of the national service guidance for urological cancers. Members of the ScHARR team attended all the Editorial Board meetings, facilitating a full understanding of the guidance as it developed.

2.2 Literature and data searching

Literature searches were carried out on MEDLINE, HMIC and Embase in order to identify any existing costing exercises, audits of cancer activity, cost of illness studies or models of treatment pathways. ScHARR also liaised with the evidence review team to make use of their extensive literature searching.

Regional cancer registries were contacted for data and information that could inform the process.

Hospital Episode Statistics (HES) data were obtained to provide an understanding of recent hospital activity on a national basis. Data were obtained for four years from 1995/6 to 1998/9. Although the data do not include clinical details such as pathology and staging, each record of admission includes information on: cancer site (diagnosis code), operation code, healthcare resource group (HRG) classification and trust. Additional analysis of HES data was undertaken by the National Cancer Services Analysis Team, which included 1999/2000 data.

Summary data was also obtained from the British Association of Urological Surgeons (BAUS) oncology section, which collects data on the diagnosis, staging, grading and treatment of new urological tumours. The data has some limitations; being collected on a voluntary basis it is estimated to have only around 60% coverage. Also, only initial treatment is included, so for some cancers treatment rates appear low.

Cost data in the form of HRG's, available from the National Reference Cost (2000) database,⁵ were obtained. HRG costs are produced by every trust in the country using a very detailed bottom-up method which costs all elements of patients' care including theatre time, laboratory tests, pathology tests, minutes of nursing time, minutes of consultant time, physiotherapy, x-rays, ultrasound, pharmacy and overheads (administration, heating etc). Data are available for inpatient elective and non-elective cases, as well as day cases.

The 2000 Reference Costs⁵ have very little information on urology outpatients, but some trusts have prepared outpatient urology costs for inclusion in the 2001 database. Although these are not yet published we were able to obtain some from a sample of hospitals. These were particularly useful for costing diagnostic procedures. While radiotherapy costs are included in the 2000 Reference costs, the distribution of costs for a particular treatment among different trusts must be very skewed as the mean cost of a treatment is often considerably less than the lower interquartile range. Advice was sought from a clinical oncologist, and costs of treatment built up from the costs of individual fractions (single treatment within a course).

Clinical and nurse staff costs were taken from Netten and Curtis.⁶ These costs include not only wages, but also overhead costs.

Very little costing data was found in the literature for the UK, and the little that there is was out of date. There are some American studies of costs, but their treatment patterns and cost structures are quite different, and where costs could be compared to UK values, for example for operative procedures, they were very different.

Where HRG costs were not available hospital trusts were contacted to obtain cost estimates.

2.3 Discussions with clinicians and other key professionals

Advice from clinicians on the Editorial Board was sought to ensure that appropriate assumptions were made in the modelling of future activity, to identify data sources and to assist in the interpretation of data. Other clinicians, particularly urologists, were contacted to assist in the development of the care pathways for the different cancers, to canvass opinion on the probability and likely scale of any increase in prostate cancer incidence, and the current state of multidisciplinary teams (MDTs). Several specialist nurses were also contacted to discuss their roles in MDTs and in patient support.

2.4 Production of conceptual models of clinical pathways

Following examination of the literature and discussions with clinicians, individual treatment pathways for patients were produced for prostate, bladder, renal, testicular and penile cancers. The pathways identify the key stages of the care process, and decision points. Production of the care pathways was helpful in developing an understanding of the patient journey, and was essential to ensure that the full consequences of a change to any element of the pathway could be considered for the whole system.

2.5 Identification of key cost issues

SCHARR used the guidance, editorial board discussions, preliminary data analysis and consultations with both clinicians and service managers to identify and prioritise the key cost issues.

2.6 Cost analysis and modeling

For each of the key issues an estimate of the national cost consequences has been made. The approach adopted for each issue is detailed in the relevant section.

3. Multidisciplinary teams

Multidisciplinary team working is intended to ensure that patients benefit from the expertise of a range of specialists for their diagnosis and treatment, and that care is given according to recognised guidelines. For some cancers, MDTs are well-established in most trusts, but for urological cancers even the concept of MDTs is not well-accepted in all trusts.

Most centres hold urology MDT meetings, and have an MDT co-ordinator to assist in collating material prior to the meeting, recording decisions during the

meeting, and disseminating the results. Most meetings are held for an hour every week, some having an additional 15 minutes available if necessary. It is usually only sufficient time to review the more complex new patients, with straightforward cases sometimes dealt with in groups. Very few cases are brought back to the team meeting to discuss management of further progression of the cancer. Some teams have problems with the lack of availability of pathologists, radiologists and palliative care consultants to attend meetings, despite their on-site presence, as these specialists are in short supply and have many demands on their time other than uro-oncology. Meetings are usually held prior to the start of the working day, or in a lunch break.

Most units also hold MDT meetings, but very few have co-ordinators, restricting their effectiveness. Those that have them often share them with several other teams, limiting what the co-ordinator can undertake. Most have problems with getting a full team together; almost all lack at least one from a pathologist, radiologist or oncologist. These consultants are not always based on-site, and some only work one session every two weeks at the unit, restricting the time available to attend meetings. Many units hold MDT meetings (also usually of one hour's duration) only every fortnight, partly because of the availability of visiting specialists.

In order to ensure that all units and centres have fully operational MDTs in accordance with the guidance, it is estimated that £3.6 million is required, to put a dedicated urology MDT co-ordinator (A&C grade 4) in place in every unit, and to allow an additional consultant session per week per unit. However, as there is a shortage of pathologists, radiologists and oncologists, it may be difficult for units to find the clinicians to fill the extra sessions in the short term. The role of MDT co-ordinator is not necessarily a full time role at unit level, but many combine the co-ordination of meetings with data collection, which is also currently under-resourced, so a full time post has been used in the costing.

The need for additional staff to allow more time for MDT meetings is not universally accepted, with the belief that it is a matter of staff goodwill to make time for the meetings. Indeed, projects undertaken as part of the Cancer Services Collaborative have shown that much can be done to improve both the efficiency of MDT meetings and attendance, by implementing agreed systems for their operation, requiring only limited additional resources. However, all existing meetings identified already take place outside the normal working day, and even those who are enthusiastic about the progress that has already been made in implementing MDTs foresee difficulties in complying with the guidance. If it is assumed that each unit will require an additional hour's meeting every two weeks, with an additional half hour preparation time, and that each centre will require an additional hour per week to discuss all patients (but with no additional preparation time), and that additional staff costs will be incurred for all members of the MDT, the cost of the additional staff time is £2.8 million. Again, shortage of staff, in particular pathologists, radiologists and oncologists, may make the acquisition of more staff difficult.

If the additional costs of staff time are allowed for, the total cost of fully implementing MDTs is £6.4 million per year.

4. Centralisation

4.1 Total costs of centralisation

The guidance recommends some centralisation of services, in particular requiring that MDTs which undertake radical prostatectomy and cystectomy should perform a combined total of at least 50 operations per year. Ideally there should be only one team per network, covering a population of at least one million people, undertaking this type of surgery. Analysis of HES data shows that this is a radical change from current practice. In 1999/2000 only three trusts undertook 50 or more prostatectomies and cystectomies, with 40 performing fewer than six.

There are also requirements that some renal, testicular and penile cancers should be referred to specialist teams. These have not been included in the analysis of the

impact of centralisation, as they will have a negligible effect on the additional workload of specialist teams. Most renal and testicular cancer patients requiring specialist attention are already referred to centres. For example, analysis of HES data from 1995/1996 - 1999/2000 showed that for patients with a diagnosis of testicular cancer, only nine trusts undertook removal of a lesion of the lung, and 13 trusts undertook para-aortic lymph node dissection. Even if a small additional proportion of patients will be referred for specialist care as a result of the guidance, the effect will be negligible as the numbers of renal and testicular cancers are relatively small (incidence of 6,280 in total for both sites). Services for penile cancers in many networks will have to change to comply with the guidance, but as the numbers are very low (less than 400 per year in England and Wales) the effect on the workload of the specialist centres will be small.

To estimate the effect of greater specialisation of services for radical prostatectomy and cystectomy, an analysis was undertaken of the current (1999/2000) number of operations by hospital, network and region, and an estimate made of the proportion of work that will have to move from units to centres in each network in order to fulfil the requirements of the guidance that a team should undertake at least 50 per year, and the ideal that there should be only one team per network covering a population of at least one million people. Different configurations are possible, so maximum and minimum scenarios were developed to cover the likely range. The assumptions on which the two scenarios are based are described below.

Maximum cost scenario (minimum number of centres)

It is assumed that there will be one centre per network, except where the network population is less than one million or the current total workload (prostatectomies and cystectomies) within the network is less than 40 (assuming those in range 40-49 will soon be doing more), in which cases the work will have to move to neighbouring networks.

Minimum cost scenario (maximum number of centres)

It is assumed that there will be a centre for each whole million population within a network, and each network with a population of more than one million will have at least one centre, even if current workload is low (less than 40). The

operations in networks with a population of less than one million all move to neighbouring networks.

For both these scenarios it is assumed that the trust(s) currently undertaking the most prostatectomies and cystectomies in the network will become the specialist centre(s). However, in practice there may be other local structures which will need to be considered in the configuration of services. This analysis does not take these into account, and is intended only to estimate the magnitude of the shift in services resulting from the guidance, and the cost implications of that shift.

As services in Wales are very dispersed, it was assumed for both prostatectomies and cystectomies that the proportion that would have to move to a centre would be the same as the maximum proportion for any English region.

In practice the number of teams which undertake prostatectomies and cystectomies is likely to be somewhere between these two scenarios. The central estimate of the total cost is based on the mid-point of the maximum and minimum estimates.

Table 4.1 Cost impact of centralisation by region

Region	% Operations to move		Additional Costs (£000s)		
	Min	Max	Min	Max	Central Estimate
1	27.49	48.94	287	504	396
2	44.33	68.47	288	430	359
3	61.07	61.07	455	455	455
4	45.88	72.76	424	621	522
5	55.02	82.01	473	672	572
6	48.35	59.80	580	682	631
7	52.54	63.68	582	739	661
8	51.27	70.55	438	558	498
England	48.41	66.54	3,526	4,662	4,094
Wales	67.50	83.70	267	317	292
Total	49.37	66.49	3,794	4,979	4,387

The additional cost is calculated on the basis of the average HRG (2000)⁵ cost of radical prostatectomy and cystectomy, and assumes that the fixed and semi-fixed proportion of the costs (83%) will not be released from hospitals giving up the work. The proportion of the cost that is variable was established by contacting trusts which undertake these operations, for their breakdown of their HRG cost by fixed, semi-fixed and variable cost elements. Not many trusts were able to provide this data, and the average variable element (17%) is based on the average of only three trusts. The range was 8% to 24%. Sensitivity analysis using this range of the proportion of variable cost gives slightly smaller variation in the estimate of the total costs of centralisation than the maximum and minimum scenarios shown in Table 4.1.

4.2 Potential cost savings from centralisation

The aim of greater specialisation of surgery is to improve outcomes for patients, and this might be expected to be reflected by shorter lengths of post-operative stay and/or lower re-admission rates. Analysis of HES data revealed no relationship between operative volumes and length of stay or re-admission rates. As the number of hospitals undertaking larger volumes (greater than 50 per year) is limited to only three hospitals, it is not surprising that no relationships were found. One study in the United States⁷ found significant inverse relationships between volumes of prostatectomies and both length of stay and re-admissions. However, the effects were small, and would have negligible cost consequences.

4.3 Impact of centralisation on individual centres

The impact on individual centres will vary considerably. The Cancer Care Alliance of Teesside, South Durham and North Yorkshire already offers a specialist service for radical prostatectomy and cystectomy, with very few of these operations undertaken anywhere other than the South Tees Hospitals NHS Trust. However the situation in this network is not representative of the whole country.

Taking the maximum cost scenario, (minimum centres), each centre is currently on average undertaking 34 operations, and will have to undertake a further 52 as a result of centralising services, an increase of 153%. This estimate of additional workload does not take into account the longer-term effect of the potential increase in the numbers of cystectomies (from more aggressive treatment of bladder cancer) and prostatectomies (resulting from increasing incidence) discussed in Sections 8 and 6 respectively. The additional surgery could result in each centre having to undertake 58 to 85 more prostatectomies and cystectomies, as well as the additional work resulting from the centralisation of services. This maximum scenario suggests that in total, by 2004, each centre may typically have to undertake 110-137 more prostatectomies and cystectomies than currently.

For the minimum cost scenario, based on the maximum possible number of teams undertaking prostatectomies and cystectomies, there is a smaller effect on the teams undertaking the work. Centralisation alone is likely to increase the number of operations on average by 39, with the total additional workload, including increases in surgery, ranging from 79 to 97.

These numbers suggest that centres undertaking prostatectomies and cystectomies will typically have to undertake an extra operation per week as a result of centralisation, but increasing demand for the operations may bring the number up to an additional two per week. These numbers are relatively small in terms of total theatre capacity, but some trusts are already experiencing difficulties with their current facilities, and the need to fit in more operations will add to the pressures.

All patients who have a cystectomy, and some who have a prostatectomy, require special nursing care for one to two days after their operation. This care is usually provided in a High Dependency Unit (HDU), but may also be provided on general wards. The costs of this care will be included in the HRG

cost, but trusts will need to consider how increases in the number of operations will increase demand for HDU beds.

5. Specialist nurses for patient-centred care

The guidance emphasises the need for improved information and support for urological cancer patients, and the central role that nurse specialists should play in delivering more patient-centred care.

Neither the role nor training for urological nurse specialists are well-defined. Some are more specialised than others being dedicated to cancer patients while others support all urological patients. The range of activities that they are involved in includes:

- Supporting patients during and after the 'bad news' interview with the clinician
- Providing patients, both orally and in writing, with information about their disease and its treatment
- Making themselves available for ongoing support by telephone
- Running haematuria clinics (sometimes including cystoscopies)
- Running prostate assessment clinics (very rarely including TRUS biopsy)
- Running follow-up prostate cancer clinics, including hormone therapy
- Intravesical therapy
- Home visits, and liaison with other carers
- Provision of advice and training for ward staff

Most specialist nurses have spent many years on urological wards, but others have come via oncology. Depending on their background they have needed training in the other aspect of specialist care. Some have attended short courses to achieve this, but many comment that the training has been 'on the job', and that there are no specialist uro-oncology courses. Most have had training in counselling, either as part of their degree course, or as a short course.

The current provision of nurse specialists is patchy. There are several specialist nurses who are providing the levels of support indicated in the guidance. However some are stretched very thinly, being solely responsible for several hundred cancer patients. Audit data from the Northwest region suggests that many patients are not being counselled by a specialist nurse, although it is impossible to distinguish between possible poor recording of nurse counselling in the patient's notes and it definitely not having been provided. The data, if accurate, shows that while most patients with localised prostate cancer had counselling from a doctor, only 11% were counselled by a nurse, and 9% received no such support. For patients who had a cystectomy for bladder cancer, less than a third had nurse counselling. There was some correlation between trusts where most patients were counselled by a nurse and the proportion who were warned of possible sexual dysfunction as a result of

cystectomy. Overall only 24% had a record of this warning in their notes. The recent report from the Commission for Health Improvement (CHI) and the Audit Commission (AC)¹ shows that only half of patients have a nurse specialist present when bad news is given.

This may be owing to lack of availability of nurses, as some trusts providing urological cancer services have no specialist nurse at all, possibly as many as 50%, according to the CHI/AC report.¹ This situation is rapidly changing, however, as several urological (cancer) nurses are currently being recruited. There is some question as to whether all the nurses recruited have sufficient experience and/or training, owing to the shortage of fully experienced staff.

Specialist urological cancer nurses have also started to seek more formal recognition of the specialisation. A support group of around 40 such nurses, which was formed four years ago, is now seeking accreditation as a recognised sub-speciality within the British Association of Urological Nurses (BAUN).

It has proved difficult both to assess exactly what additional nursing resources will be required, and what the training requirements will be. To provide an order of magnitude estimate the following assumptions will be made. The CHI/AC report indicates that only 50% of trusts providing a urological cancer service have a nurse specialist,¹ but as the situation is changing rapidly with nurses being appointed, it will be assumed that it is only 30% of trusts that are still without a specialist nurse. For the 70% of trusts that are assumed already to have at least one nurse it will be assumed that on average they need 30% more nursing resource, on the basis that around 30% of specialist urological cancer nurses reported severe time constraints on the service that they could provide.¹

On the basis of these assumptions around 80 more nurse specialists will be required, at an annual cost of £2.68 million. If it is assumed that these additional nurses will need to complete a post-registration diploma in oncology nursing (ENB 237) the training cost is £0.32.

6. Potential increase in incidence of prostate cancer

Figure 1 (See *Improving Outcomes in Urological Cancer – The Manual, Background*) in the main report shows the incidence and mortality from prostate cancer over the last 30 years for England and Wales. After several years of a steady increase in incidence, there was a steep rise in the early 1990s taking the incidence to a maximum of around 70 per 100,000 of the male population. The incidence of prostate cancer increased through the mid 1990s⁴ and the latest data, for England and Wales for 1998, shows an increase of 2,300 over the previous year.^{2,3} Mortality from prostate cancer appears to be declining slightly after several years of steady increase.

Recorded incidence is a function of two separate parameters - underlying disease incidence and detection rates. Several studies have attempted to identify to what extent the increasing incidence of reported cancers, seen until recently, was due to the two separate factors. Their conclusions as to whether the underlying incidence is increasing vary, but all agree that increased testing, in particular PSA testing, has had an effect.

Given that it has been established from post-mortem that many elderly men have undetected prostate cancer, and that in the short term the effect of any change in the underlying rate is likely to be small compared to the effect of changes to testing for prostate cancer, it will be assumed that the underlying incidence rate is constant for the purposes of estimating the numbers of patients who will be diagnosed with prostate cancer in the next few years. Sensitivity analysis around the uncertainties of changes in incidence rate owing to testing are likely to cover any uncertainty as to changes in the underlying incidence rate.

The effect of population ageing in the short term (next five years) only has a small effect on incidence.

6.1 Changes in PSA testing rates and the potential effect on incidence

In order to estimate how incidence may change as a result of changes to PSA testing rates it is necessary to establish what has happened in the past. Unfortunately there is no routine data on the extent of PSA testing. However a study has been undertaken by Melia and Moss based on a 1998/9 general practice database.⁸ This study identified how many men aged over 44 who had no prior record of prostate cancer had a PSA test that year. Chamberlain et al reported a similar study for 1994.⁹ The results of these are shown below (Table 6.1.1), together with predicted rates of testing in 1997 and 2001 based on the increase from 1998 to 1999.

The table also shows what the current incidence may be, given the estimated PSA testing rate, and assuming that 3.3% of tested men will have a cancer identified. The latter estimate of detection rate is based on preliminary findings of the ProTeCT trial for men aged under 70 (2.1%) and clinician estimate for men aged over 70 (5%).¹⁰ The proportion of tests for each age group is derived from Melia.⁸

Table 6.1.1 PSA Testing Rates and Incidence of Prostate Cancer

Year	% Men aged >44 PSA tested per year	Source	Prostate cancers in England & Wales
1994	1.4	Chamberlain ⁹	
1997	2	Projection 1	18,300
1998	2.7	Melia ⁸	20,500*
1999	3.5	Melia ⁸	
2001	5.1	Projection 1	25,000-28,000
2004	9.6-12.2	Projection 2	45,000

* 1998 incidence is based on provisional England figures for 1998 plus Wales 1997.

Projection 1: based on change 1998 to 1999.

Projection 2: American age-specific incidence applied to England and Wales population, likely PSA testing levels to obtain incidence.

There is a level of uncertainty in the projected figures, in particular those for 2004.

Apart from the uncertainty around PSA testing levels, there is also uncertainty about the number of cancers that will be detected *without* PSA testing, and how that is likely to change. It has been common practice to examine chips of tissue removed during transurethral resection of the prostate (TURP) for evidence of cancer. The procedure was common for the relief of benign prostatic hyperplasia (BPH), but is also undertaken for cancer patients. The finding of incidental cancers is reported to be between 14% and 18%.⁹ The number of patients receiving TURP has declined significantly from 53,327 in 1993/3 to 32,276 in 1999/2000, and this decline may explain why prostate cancer incidence was stable through the mid 1990s, despite the increase in PSA testing. Another reason why incidence may not have risen initially could be if the increase in PSA testing by GPs was mainly for symptomatic patients, whom the GP would have referred for investigation anyway, rather than for screening. An unpublished survey of GPs reported by Dearnaley¹¹ showed that in 1998 only 52% of GPs gave a PSA test to asymptomatic men who requested one, and there was less public awareness of the test than there is now, so it is likely that fewer requests were made.

It appears that cancer incidence may now be starting to rise, although the last available figures are for 1998, so it is not known exactly what is currently happening. However, most urologists believe that incidence is increasing as a result of PSA testing; some report a four to five-fold increase in prostate biopsies over the last five years. Awareness of prostate cancer is increasing, and national policy has recently changed to allow men to have a PSA test on request, after counselling. American incidence levels are considered plausible. If age-specific American incidence rates (1994 to 1998) for white males (rates for Afro-Caribbeans are higher, but they comprise only 2% of the population) are applied to the population of England and Wales, this gives an incidence of 45,000, more than twice the last reported figure (1998).¹²

The proportion of men who would need to be PSA tested to achieve American incidence levels has been estimated assuming a detection rate of 3.3%, as described above, with two different estimates of the number of non-PSA detected cancers. For the lower estimate of the proportion of men PSA tested each year (9.6%) it has been assumed that the estimated number of non-PSA detected cancers for 1998 will remain the same at around 12,000. They would therefore comprise 30% of the total of prostate cancers detected, which is a similar proportion to that which has been reported in the US.¹³ The high estimate of the proportion of men PSA tested each year is based on only 4,000 cancers a year being detected by other means, an estimate of the number of cancers with non-GP referral in 1998 (derived from BAUS data proportions). This gives a high estimate of 12.2%.

A PSA testing rate of up to 12.2% of men per year seems plausible, even without individual invitations for a test. In the Austrian Tyrol study 32% of men responded to a general invitation through the media for PSA testing.¹⁴ Public awareness of prostate cancer is increasing, women's magazines having reputedly made a major contribution.

In the United States PSA testing rates are considerably higher, with 48% of men aged 40+, and 73% of men aged 65+ having a PSA test each year.¹³ With this level of testing detection rates must be considerably lower. Incidence and mortality rates have now started to fall in the USA, but only very slightly, and

after a few years of high levels of PSA testing. No immediate reduction in detection rates or mortality will be assumed.

6.2 Patient age group and stage of additional cancers detected

The current (1997) numbers by age group (less than 70 years of age or greater than 70 years of age) and stage were estimated by applying BAUS data (1997) on stage to 1997 incidence data. To estimate what the numbers would be if incidence rose to American levels, National Cancer Database (NCDB) data on staging was applied to the predicted incidence.¹⁵ The numbers are shown in Table 6.2.1. Note the NCDB data uses American Joint Committee on Cancer (AJCC) staging. This has been assumed to be equivalent to BAUS staging, with the exception of AJCC stage 0 which has been included with AJCC stage 1 into BAUS stage 1.

Table 6.2.1 Age and stage of additional prostate cancers

	England & Wales 1997			American rates			Difference		
	Age <70	Age 70+	Total	Age <70	Age 70+	Total	Age <70	Age 70+	Total
Stage 1	131	321	4,25	5,596	5,880	1,1476	5,464	5,559	11,023
Stage 2	3,060	4,422	7,482	1,0138	1,0653	2,0791	7,078	6,231	13,309
Stage 3	984	2,767	3,751	2,589	2,721	5,310	1,605	-46	1,560
Stage 4	838	2,391	3,229	1,799	1,891	3,690	961	-500	461
Unknown*	1,138	2,247	3,386	1,821	1,914	3,735	683	-333	350
Total	6,152	12,148	18,300	21,944	23,059	45,003	15,792	10,911	26,703

* Assumes unknown proportion is the same for both age groups

It can be seen that the majority of the additional prostate cancers potentially identified by increased PSA testing are localised (stage 1 and 2), with approximately half of them in the under 70s, where radical treatment is more likely to be considered.

6.3 Scenarios for estimation of additional costs arising from the detection and treatment of prostate cancer

Low increase scenario

The low scenario is based on a steady increase in the number of cancers between 2001 and 2004, assuming that the increase between 1997 and 1998 continues. Note that on its own such an increase would not be significant, but in the context of the general consensus that incidence rates are rising and will continue to rise, it is being assumed that the trend will continue. This assumption yields a total incidence of 33,500 by 2004, an estimated increase of 8,700 from 2001.

High increase scenario

The high scenario is based on a steady increase, as described in the low scenario, until 2001. It is then assumed that PSA testing rates will increase more rapidly to give American level incidence of 45,000 by 2004. This is an estimated increase of 16,900 cancers from 2001.

Central increase scenario

This scenario is based on the mid-point estimates for 2001 (incidence 26,400) and 2004 (37,600), giving an increase of 11,200. The same increase is obtained if it assumed that cancer numbers have already increased rapidly, and that American levels are reached by 2004.

The costs of the additional detection and treatment of prostate cancers, based on the scenarios described above, and assuming that all additional cancers are early stage, are shown in Table 6.3.1.

Table 6.3.1 Increased annual detection and treatment costs as a result of raised prostate cancer incidence

Scenario	Cost (£ million)		
	Low	Central	High
Additional PSA tests	6.92	17.2	27.29
Biopsies	3.44	4.46	6.71
Bad news interview			
Cancer	0.38	0.49	0.74
No cancer	0.17	0.22	0.33
Treatment consultation	0.23	0.29	0.44
Treatment			
Monitoring	0.64	0.83	1.25
Prostatectomy			
Radiotherapy	1.51	1.96	2.95
Total	15.4	28.19	43.84

The range of expected additional cost is extremely wide, from around £15 to £44 million. This reflects the degree of uncertainty as to what will happen to prostate cancer incidence in the next three years.

7. Other prostate cancer costs

7.1 Impact of MRI for all patients who receive radical therapy for prostate cancer

Discussions with urologists suggested that most do not request MR scans routinely for patients being considered for radical treatment for localised prostate cancer. Audit data from the North West region showed that about 30% of patients who had radical prostatectomy had an MRI, with almost none having had a CT scan either. It was possible to infer from the data that the situation for radical radiotherapy is similar.

The calculation of the additional number of MR scans that will be required if all patients with localised cancer have a scan prior to radical treatment is as follows. The proportion of cancers by age and stage from BAUS data were applied to the total number of new prostate cancers in 1998, in order to estimate the proportions that are localised in patients aged less or more than 70. The different age groups are used since patients in the younger age group are more likely to seek radical treatment, and in particular surgery, than the older age

group. In order to take into account the possible increase in prostate cancer since 1998 the incidence scenarios described in Section 6 were used. It has been assumed that 40% of localised cancers in patients aged <70 will be treated radically, and 20% in patients aged >70. The numbers derived from these assumptions are shown in Table 7.1.1. The number of additional MR scans is estimated to be 70% of the total expected to choose radical treatment, assuming that 30% of patients already have a scan.

Table 7.1.1 Additional requirement for MR scans for prostate cancer

Number patients/treatments	1998	2001 low	2001 mid	2001 high
Total prostate cancers	20,465	24,795	26,350	27,904
Localised, aged < 70	4,380	6,545	7,322	8,099
Localised, aged 70+	6,508	8,673	9,450	10,227
Radical therapy, aged <70	1,752	2,618	2,929	3,240
Radical therapy, aged 70+	1,302	1,735	1,890	2,045
Total radical therapy	3,053	4,352	4,819	5,285
Additional MRI	2,137	3,047	3,373	3,700
Cost	£232,978	£332,092	£367,674	£403,257

If the incidence of prostate cancer were similar now to what it was in 1998 the additional cost of MRI would be £0.23 million per year. However if incidence has risen, as is probable, the cost may be in the region of £0.37 million.

In this section the cost of all patients having an MR scan prior to radical treatment, based on the estimated number of patients in this category in 2001, has been estimated. The cost of additional MR scans if prostate cancer incidence increases over the next three years is included in Section 6, where different prostate incidence scenarios are considered.

7.2 Costs of unnecessary bone scans

Some patients are currently having bone scans unnecessarily. According to the guidance, bone scans are unlikely to be useful in previously untreated patients with PSA below 10ng/ml and Gleason score below 8. Audit data from the North West of England shows 45% of patients with localised prostate cancer having a bone scan, of which a third are for patients with a PSA of less than 10ng/ml and Gleason score below 8. This means that 14% of patients with localised prostate cancer are having a bone scan which is probably unnecessary. There was considerable variation in practice between the different hospitals in the North West. The proportion of patients having a bone scan, which judging by the patients' PSA levels and Gleason score appeared to be unnecessary, varied from 0% to 60%.

The table shows the potential cost saving if no patients with PSA less than 10ng/ml and Gleason score below eight has a bone scan, assuming that the average for the North West of 14% of localised cancers is applicable to the whole country.

With prostate cancer incidence at the levels predicted for 2001 the potential cost saving is £0.53 million. If the number of early prostate cancers rises further over the next few years the potential savings from ensuring that only patients likely

to benefit are given a bone scan are even greater. The savings will be greatest in those trusts where most patients are currently given a bone scan routinely.

7.3 Conformal radiotherapy

The guidance states that centres should aim to provide conformal radiotherapy.

There are two different methods of providing conformal radiotherapy. Low melting point alloy blocks can be added manually to a traditional linear accelerator to shape the beam. This method allows conformal therapy to be provided without purchasing a new treatment machine, but requires more setting-up time for each patient than new machines. The new machines have multi-leaf collimators (MLC's), a device with numerous 'fingers' that shape the beam, added onto the linear accelerator. These machines are quicker to set up for conformal therapy.

In an audit by the national cancer services analysis team (www.cancernw.org.uk) undertaken at the start of 2001, 84 working linear accelerators capable of providing conformal radiotherapy by multi-leaf collimator existed. This figure is thought to be an underestimation since hospitals are currently investing in new machines, and hospitals known to have linear accelerators with MLC are not on the list. The audit did not record where low melting point alloy blocks were being used to provide conformal radiotherapy with traditional linear accelerators. However, this method of providing conformal radiotherapy is being phased out as old machines are replaced. Many new machines are already pre-ordered in next year's budgets. Since conformal radiotherapy is used in treatments other than for prostate, and machines are generally available, or being installed, the cost of the provision of new machines has not been included.

However, conformal therapy does require extra planning and treatment time, and so will lead to additional staff costs. An estimate has been made to cost the extra time needed to provide conformal, rather than traditional, radiotherapy.

Costs of planning radiotherapy

Table 7.3.1 shows the time required from various staff for different elements of treatment planning. The actual times required for each patient will vary, but those shown below are indicative of what is needed for the different treatments. Note conformal treatments also require more time for the verification of the conformal shielding, and also for ensuring patient position reproducibility, than for external beam therapy, but it has not been possible to quantify the additional time.

Table 7.3.1 Time required for treatment planning

Procedure	Time (minutes)		Staff Involved
	Conformal	Non-conformal	
Preparation of CT data for outlining	20	20	Superintendent 2 or 3 Radiographer
Outlining of clinical target volume	40	20	Consultant Clinical Oncologist
	40	20	Superintendent 2 or 3 Radiographer
Planning	30	15	Superintendent 2 or 3 Radiographer
Physics checking	30	15	B or C Grade Physicist
Total	160	90	

The estimated staff costs per hour (including salary and additional staff costs such as pension, overheads and training) are shown in Table 7.3.2. Radiographer and physicist costs are variable between trusts.

Table 7.3.2 Hourly staff costs

Staff	Cost per Hour (£)
Superintendent 2 or 3 radiographer (estimated)	24.68
Consultant clinical oncologist	81.89
B or C grade physicist (estimated)	23.18

Using the planning times and costs per hour shown in the tables above gives a planning cost of conformal radiotherapy of £103, compared to £56 for non-conformal external beam.

Cost of treatment

A normal course of radiotherapy for prostate cancer is 33 fractions (33 separate treatments). Both conformal and non-conformal therapy can be related to HRG codes, but both belong to codes grouped as >23 fractions, so the cost of treatment for prostate cancer is likely to be greater than the HRG codes indicate. Table 7.3.3 shows both the HRG costs and local costs for Nottingham. The latter are built up from the cost per fraction and are therefore likely to be more representative of the costs specific to prostate cancer. The Nottingham costs have been used in our estimates.

Table 7.3.3 Cost of course of radiotherapy treatment

Radiotherapy method	Local Nottingham costs (£)	HRG mean costs (£) (greater than 23 fractions)
Conformal MLC (HRG w16)	660	301
Conformal low melting point alloy blocks (HRG w23)	1,122	460
Standard radiotherapy (HRG w08)	495	288

Total cost of radiotherapy

Combining the costs of planning and treatment for the different forms of radiotherapy gives the total costs shown in Table 7.3.4.

Table 7.3.4 Total cost of radiotherapy treatment

Radiotherapy Method	Planning	Treatment	Total
Conformal MLC	£103	£660	£763
Conformal low melting point alloy blocks	£103	£1,122	£1,225
Standard radiotherapy	£56	£495	£551

Proportion of patients having radical conformal rather than standard radiotherapy of the prostate

A survey was conducted of radiotherapy services managers/superintendent therapy radiographers in the south. Many of the respondents indicated that they were already treating all their patients with conformal radiotherapy, but most respondents were from large centres, so the response may well be biased. Some are using low melting point alloy blocks, rather than MLC. A few said that no patients were given conformal radiotherapy. It was impossible to determine with any accuracy what the current proportions are of patients having each form of radiotherapy from their responses.

However, in order to provide an order of magnitude estimate of what may be the impact of all patients having conformal radiotherapy, it has been assumed that currently the proportions of MLC, low melting point alloy blocks and standard radiotherapy are 30%, 15% and 55%. The numbers of patients requiring radical therapy are as shown in section 7.1 (MRD). It is assumed that all patients aged over 70, and half of patients aged under 70 will have radiotherapy rather than surgery. The results of the analysis based on these assumptions are shown in Table 7.3.5.

Table 7.3.5 Additional cost of all radical radiotherapy for prostate cancer being conformal

	1998	2001 low	2001 mid	2001 high
Total cancers	21,465	24,795	26,350	27,904
Additional cost	£102,997	£143,958	£158,664	£173,370

This suggests that the additional costs of ensuring that all patients having radical radiotherapy are treated with multileaf conformal therapy are relatively small, assuming that new multi-leaf collimator machines are made available. This is partially because cost savings are derived from the phasing out of low melting point alloy treatment, which is more expensive than multi-leaf.

8. Bladder cancer

This analysis relies heavily on audit data collected in the North West region in the year 2000, as well as using national HES data. Preliminary results from an audit of muscle invasive cancers in the South West region also confirms the general picture that these cancers are more actively treated than in the past, although there are still delays in patients receiving treatment.

The total number of cancers by clinical stage at diagnosis is shown in Table 8.1. The total number of cancers is for England and Wales 1997, and the proportions of cancers by stage are derived from the BAUS data. The proportions derived from the North West audit data are similar.

Table 8.1 Bladder cancer stage

Clinical stage		Percent	Number
Superficial	low risk	45	5,436
	high risk	23	2,778
Muscle invasive		32	3,866
Total cancers		100	12,080

Inadequate staging

The North West data show that 16% of patients diagnosed with superficial cancer did not have any muscle taken when they had their initial biopsy, nor was there an early repeat biopsy, so their staging was inadequate. The cost of 16% of superficial bladder cancer patients having an additional biopsy is £0.2 million per year. These cancers may be upstaged as a result of the repeat biopsy, but the possible additional treatment costs will be covered in the radical treatment section.

Low risk superficial cancers

There is evidence that not all patients (40%) are receiving single shot chemotherapy after their endoscopic resection. The cost of additional single shot therapy for these patients is £0.45 million per year.

High risk superficial cancers

These cancers include grade 3 superficial tumours, carcinoma in situ and extensive, recurrent or multifocal G2 tumours. These patients are at higher risk of their cancer progressing, despite the tumour being superficial. There is a general belief that these cancers are not as aggressively treated as they ought to be, which is confirmed by the North West audit data. This shows that 36% of patients had nothing more than a check cystoscopy.

As a minimum these patients should have a course of intravesical BCG treatment. This would cost £1.59 million. Some of these patients will fail to respond to BCG therapy, or their cancer will recur, and they may need further radical therapy.

Table 8.2 Current treatment for high risk superficial bladder cancers

Treatment	%
Course intravesicle therapy	45
Cystectomy	4
Radiotherapy	16
No additional therapy	36

Radical treatment

Radical treatment, which includes cystectomy and radical radiotherapy, is usually carried out for muscle invasive cancers, but high risk superficial cancers may also need radical treatment. A study of muscle invasive bladder cancers in the South West region in 1993 showed that almost half of patients had no definitive treatment, which could include either radical therapy or palliative radiotherapy.¹⁶ Recent data from the North West indicates that the situation has improved considerably; 15% of patients had no treatment, of whom half were recorded as being unfit for treatment.

However there is still some evidence that not all patients are being offered a cystectomy when they may benefit from one. In the North West the proportion of patients who have radical cystectomy and radical radiotherapy is similar, whereas in Yorkshire 75% of patients had radical radiotherapy for muscle invasive cancer, compared to 25% who had cystectomy.¹⁷ There is no clear benefit of one treatment over the other, but these figures suggest that not all patients may be given the choice of surgery. Comparison of the number of cystectomies from HES data with the total number of bladder cancers per year shows that 13% of patients have a cystectomy. That proportion is equivalent to half the proportion of patients diagnosed with muscle invasive bladder cancer. However, other patients whose cancers have progressed after an initial diagnosis of superficial cancer, or after non-operative treatment, may benefit from a cystectomy. It is difficult to predict exactly what the operative level should be, but it is estimated that around 20% of all bladder cancer patients may benefit from cystectomy at some stage. This would mean 846 additional cystectomies a year, at a cost of £3.89 million.

Diagnostic testing prior to treatment

The guidance states that all patients should have an MR scan to assess the extent of the tumour before radical treatment. The North West data suggests that only 10% of patients have no cross-sectional imaging (CT or MRI) prior to radical treatment, but of the 90% that do, half have a CT scan rather than MR. The cost of CT and MR are similar, so the change will not have cost implications. However, if more cystectomies are undertaken, around half of which may be in patients who would formerly not have been offered radical therapy, and also allowing for the 10% of patients who currently have no cross-sectional imaging, the annual additional cost of MRI imaging is £0.09 million.

In total the cost of improving diagnosis and treatment of bladder cancer will cost £6.21 million per year.

9. Conclusions

It is estimated that the total additional cost per year for caring for urological cancer patients will be around £48 million, with a range of £34-£64 million. However, most of this additional cost will arise from a projected increase in the incidence of prostate cancer as a result of more men having screening with the PSA test, rather than from the guidance itself. Uncertainty about how rapidly prostate cancer incidence will rise is the reason for the wide range of the cost estimate.

There is considerable uncertainty around how quickly incidence will rise, and the estimated range of annual additional cost for diagnosis and treatment of these cancers ranges from £15 to £44 million by 2004, with a central estimate of £28 million.

Excluding the costs of rising prostate cancer incidence, it is estimated that the guidance, once implemented, will require expenditure of an additional £20 million per year on urological cancer patients.

The greatest additional cost - £6.4 million - arises from ensuring that MDTs are properly resourced. This includes £2.0 million for additional MDT co-ordinators, with the rest covering additional staff time. While holding regular meetings is partly a matter of organisation and of acceptance of MDTs as valuable to all concerned, many trusts will struggle to meet the requirements of the guidance without additional resources.

Despite improvements in the treatment of bladder cancer, it appears that not all cancers are treated as aggressively as they could be. It will cost an additional £6.2 million a year, principally to provide additional intravesical therapy and surgery.

The central estimate for the costs of centralising of services to ensure that patients having a radical prostatectomy or cystectomy are treated by a specialist MDT is estimated to be £4.4 million, with a range of £3.8 to £5.0 million, depending on the different possible configurations of services within networks. These estimates assume that the variable element only (17%) of the costs of surgery will be released from the trusts that currently undertake the work.

With the wide range of activities undertaken by different specialist nurses it proved difficult to quantify the costs of ensuring that specialist nurse support is available to all urological cancer patients. An order of magnitude estimate of the additional number of nurses required was made, based on survey results in the recent CHI/Audit Commission report¹ and qualitative comments from nurses and service managers. On this basis it is estimated that around 80 more nurse specialists will be required, at an annual cost of £2.68 million. If it is assumed that these additional nurses will need to complete a post-registration diploma in oncology nursing (ENB 237) the training cost is £0.32 million.

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