National Collaborating Centre for Cancer

Bladder cancer

Bladder cancer:

diagnosis and management

NICE Guideline 2

Full Guideline

February 2015

Update information

May 2021: Link added to NICE Pathway on bladder cancer for information on genomic biomarker-based therapy in solid tumour treatment pathways.
July 2019: Amended recommendations 1.1.6, 1.7.7 and 1.7.8 to add details of related NICE guidance.
The current version of the recommendations can be seen at www.nice.org.uk/guidance/NG2

Final Version

Commissioned by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Key priorities for implementation

- **Use a holistic needs assessment to identify an individualised package of information and support for people with bladder cancer and, if they wish, their partners, families or carers, at key points in their care such as:**
  - **when they are first diagnosed**
  - **after they have had their first treatment**
  - **if their bladder cancer recurs or progresses**
  - **if their treatment is changed**
  - **if palliative or end of life care is being discussed.**

- **Offer white-light-guided TURBT with one of photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker test (such as UroVysion using fluorescence in-situ hybridization [FISH], ImmunoCyt or a nuclear matrix protein 22 [NMP22] test) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT.**

- **Consider CT or MRI staging before transurethral resection of bladder tumour (TURBT) if muscle-invasive bladder cancer is suspected at cystoscopy.**

- **Ensure that for people with non-muscle-invasive bladder cancer all of the following are recorded and used to guide discussions, both within multidisciplinary team meetings and with the person, about prognosis and treatment options:**
  - **recurrence history**
  - **size and number of cancers**
  - **histological type, grade, stage and presence (or absence) of flat urothelium, detrusor muscle (muscularis propria), and carcinoma in situ**
  - **the risk category of the person's cancer (see section 4.1.2)**
  - **predicted risk of recurrence and progression, estimated using a risk prediction tool.**

- **Offer people with suspected bladder cancer a single dose of intravesical mitomycin C given at the same time as the first TURBT.**

- **Offer the choice of intravesical BCG (Bacille Calmette-Guérin) or radical cystectomy to people with high-risk non-muscle-invasive bladder cancer, and base the choice on a full discussion with the person, the clinical nurse specialist and a urologist who performs both intravesical BCG and radical cystectomy. Include in your discussion:**
  - **the type, stage and grade of the cancer, the presence of carcinoma in situ, the presence of variant pathology, prostatic urethral or bladder neck status and the number of tumours**
  - **risk of progression to muscle invasion, metastases and death**
  - **risk of understaging**
  - **benefits of both treatments, including survival rates and the likelihood of further treatment**
  - **risks of both treatments**
  - **factors that affect outcomes (for example, comorbidities and life expectancy)**
  - **impact on quality of life, body image, and sexual and urinary function.**

- **Discharge to primary care people who have had low-risk non-muscle-invasive bladder cancer and who have no recurrence of the bladder cancer within 12 months.**

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- **Offer people with intermediate-risk non-muscle-invasive bladder cancer cystoscopic follow-up at 3, 9 and 18 months, and once a year thereafter.**

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

- **Offer a choice of radical cystectomy or radiotherapy with a radiosensitiser to people with muscle-invasive urothelial bladder cancer for whom radical therapy is suitable. Ensure that the choice is based on a full discussion between the person and a urologist who performs radical cystectomy, a clinical oncologist and a clinical nurse specialist. Include in the discussion:**
    - **the prognosis with or without treatment**
    - **the limited evidence about whether surgery or radiotherapy with a radiosensitiser is the most effective cancer treatment**
    - **the benefits and risks of surgery and radiotherapy with a radiosensitiser, including the impact on sexual and bowel function and the risk of death as a result of the treatment.**

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Key research recommendations

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

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

- **In people with high-risk non-muscle-invasive bladder cancer, are these follow-up regimens equally effective in terms of identification of progression, cost effectiveness and health-related quality of life?**
    - **Cystoscopic follow-up at 3, 6, 12, 18, 24, 36 and 48 months, and then annually, interspersed with non-invasive urinary tests.**
    - **Cystoscopic follow-up at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42 and 48 months, and then annually thereafter.**

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

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

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Methodology

What is a clinical guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and onto more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Who is the guideline intended for?

This guideline does not include recommendations covering every detail of the diagnosis and treatment of bladder cancer. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing clinical evidence based questions'.

This guideline is relevant to all healthcare professionals who come into contact with people with bladder cancer, as well as to the people with bladder cancer themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care to this group of people.

The remit of the guideline

Involvement of Stakeholders

Key to the development of all NICE guidelines are the relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2012). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the bladder cancer guideline can be found in Appendix F.

The guideline development process – who develops the guideline?

Overview

The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE 2012). A team of health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG) (Appendix F), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline
- forming the GDG

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- developing clinical questions
- identifying the health economic priorities
- developing the review protocol
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- consultation and validation

The scope

The scope was drafted by the GDG Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2012). The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C
- inform professionals and the public about the expected content of the guideline
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the clinical questions and search strategies

Before the guideline development process started, the draft scope was presented and discussed at a stakeholder workshop. The list of key clinical issues were discussed and revised before the formal consultation process. Further details of the discussion at the stakeholder workshop can be found on the NICE website (www.nice.org.uk).

The scope was subject to a three week stakeholder consultation in accordance with NICE processes. The full scope is shown in Appendix E. During the consultation period, the scope was posted on the NICE website. Comments were invited from registered stakeholder organisations and NICE staff. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed and signed off by NICE and posted on the NICE website.

The Guideline Development Group (GDG)

The bladder cancer GDG was recruited in line with the 'NICE guidelines manual' (NICE 2012). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and shortlisted candidates were interviewed in person prior to being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Details of the adverts were sent to the main stakeholder organisations, cancer networks and patient organisations/charities (Appendix F). Individual GDG members were selected for telephone interview by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from

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the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix F).

Guideline Development Group Meetings

Fourteen GDG meetings were held between 18-19 October 2012 and 10-11 November 2014. During each GDG meeting (held over either 1 or 2 days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations before presenting it to the GDG. These recommendations were then discussed and agreed by the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer Representatives

Individuals with direct experience of bladder cancer services gave an important user focus to the GDG and the guideline development process. The GDG included two patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Expert Advisers

During the development of the guideline the GDG identified an area where there was a requirement for expert input on a particular specialist clinical question. An expert was identified by the NCC-C (Appendix F) and was invited to advise the GDG on drafting their recommendations for that clinical question.

Developing clinical evidence-based questions

Background

Clinical guidelines should be aimed at changing clinical practice and should avoid ending up as ‘evidence-based textbooks’ or making recommendations on topics where there is already agreed clinical practice. Therefore the list of key clinical issues listed in the scope were developed in areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

From each of the key clinical issues identified in the scope, the GDG formulated a clinical question. For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: P – the population (the population under study), I – the interventions (what is being done), C – the comparison (other main treatment options), O – the outcomes (the measures of how effective the interventions have been).

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Review of Clinical Literature

Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: NHS Evidence, Cochrane Databases of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), Health Economic Evaluations Database (HEED), Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Developing the review protocol

For each clinical question, the information specialist and researcher (with input from other technical team and GDG members) prepared a review protocol. This protocol explains how the review was to be carried out (Table 1) in order to develop a plan of how to review the evidence, limit the introduction of bias and for the purposes of reproducibility. All review protocols can be found in the evidence review.

Table 1: Components of the review protocol

Component	Description
Clinical question	The clinical question as agreed by the GDG
Rationale	An explanation of why the clinical question is important. For example, is the topic contentious? Is there variation in practice across the UK?
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework for questions about treatment, or other suitable framework for questions about diagnosis or prognosis. Including the study designs selected.
How the information will be searched	The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. (Searches should not necessarily be restricted to RCTs.)
The review strategy	The method that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.

Searching for the evidence

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on 'Incorporating Health Economic Evidence').

Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when necessary. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1946 onwards
- Excerpta Medica (Embase) 1974 onwards
- Web of Science [specifically Science Citation Index Expanded

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- (SCI-EXPANDED) 1899 onwards and Social SciencesCitation Index (SSCI) 1956 onwards]

Subject specific databases used for certain topics:

- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1937 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- Psychinfo 1806 onwards

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6-8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, June 2014 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review.

Critical Appraisal and Evidence Grading

Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. When papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. For each question, data were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All evidence was considered carefully by the GDG for accuracy and completeness.

GRADE (Grading of Recommendations, Assessment, Development and Evaluation)

For interventional questions, studies which matched the inclusion criteria were evaluated and presented using GRADE (NICE 2012; http://gradeworkinggroup.org/). Where possible this included meta-analysis and synthesis of data into a GRADE ‘evidence profile’. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (very low, low, moderate or high) as well as an estimate of the size of effect. A narrative summary (evidence statement) was also prepared.

Each outcome was examined for the quality elements defined in Table 2 and subsequently graded using the quality levels listed in Table 3. The reasons for downgrading or upgrading specific outcomes were explained in footnotes.

Table 2: Descriptions of quality elements of GRADE

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect
Inconsistency	Inconsistency refers to unexplained heterogeneity of results
Indirectness	Indirectness refers to differences in study population, intervention, comparator or outcomes between the available evidence and clinical question
Imprecision	Results are imprecise when studies include relatively few events and when the confidence interval around the effect estimate includes both no effect and appreciable benefit or harm

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Quality element	Description
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2012). In general, no formal contact was made with authors.

For non-interventional questions, for example the questions regarding diagnostic test accuracy, a narrative summary of the quality of the evidence was provided. The quality of individual diagnostic accuracy studies was assessed using the QUADAS-2 tool (Whiting et al., 2011).

Needs Assessment

As part of the guideline development process the NCC-C undertook a needs assessment. This aims to describe the burden of disease and current service provision for people with bladder cancer in England and Wales, and informed the development of the guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented early in the stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

Incorporating health economics evidence

The aim of providing economic input into the development of the guideline was to inform the GDG of potential economic issues relating to bladder cancer. Health economics is about improving the health of the population through the efficient use of resources. In addition to assessing clinical effectiveness, it is important to investigate whether health services are being used in a cost effective manner in order to maximise health gain from available resources.

Prioritising topics for economic analysis

After the clinical questions had been defined, and with the help of the health economist, the GDG discussed and agreed which of the clinical questions were potential priorities for economic analysis. These economic priorities were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2012):

- the overall importance of the recommendation, which may be a function of the number of patients affected and the potential impact on costs and health outcomes per patient

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- the current extent of uncertainty over cost effectiveness, and the likelihood that economic analysis will reduce this uncertainty
- the feasibility of building an economic model

A review of the economic literature was conducted at scoping. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence.

For systematic searches of published economic evidence, the following databases were included:

- Medline
- Embase
- NHS Economic Evaluation Database (NHS EED)
- Health Technology Assessment (HTA)
- Health Economic Evaluations Database (HEED)

Methods for reviewing and appraising economic evidence

The aim of reviewing and appraising the existing economic literature is to identify relevant economic evaluations that compare both costs and health consequences of alternative interventions and that are applicable to NHS practice. Thus studies that only report costs, non-comparative studies of 'cost of illness' studies are generally excluded from the reviews (NICE 2012).

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE 2012; Appendix H). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the GDG for a specific topic within the guideline. There are two parts of the appraisal process; the first step is to assess applicability (i.e. the relevance of the study to the specific guideline topic and the NICE reference case) (Table 4).

Table 4: Applicability criteria

Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e. the methodological quality, Table 5).

Table 5: Methodological quality

Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

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Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

If high-quality published economic evidence relevant to current NHS practice was identified through the search, the existing literature was reviewed and appraised as described above. However, it is often the case that published economic studies may not be directly relevant to the specific clinical question as defined in the guideline or may not be comprehensive or conclusive enough to inform UK practice. In such cases, for priority topics, consideration was given to undertaking a new economic analysis as part of this guideline.

Economic modelling

Once the need for a new economic analysis for high priority topics had been agreed by the GDG, the health economist investigated the feasibility of developing an economic model. In the development of the analysis, the following general principles were adhered to:

- the GDG subgroup was consulted during the construction and interpretation of the analysis
- the analysis was based on the best available clinical evidence from the systematic review
- assumptions were reported fully and transparently
- uncertainty was explored through sensitivity analysis
- costs were calculated from a health services perspective
- outcomes were reported in terms of quality-adjusted life years

Linking to NICE technology appraisals

There is a published technology appraisal (TA) which is relevant to this guideline (TA272 - see www.nice.org.uk/TA/published). In line with NICE methodology, the recommendations from this TA have been cross referenced in the bladder cancer guideline.

Agreeing the recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicitly in the accompanying linking evidence to recommendations (LETR) statement (see below).

Wording of the recommendations

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made. Some recommendations were made with more certainty than others. Recommendations are based on the trade-off between the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence.

For all recommendations, it is expected that a discussion will take place with the patients about the risks and benefits of the interventions, and their values and preferences. This discussion should help the patient reach a fully informed decision. Terms used within this guideline are:

- ‘Offer’ – for the vast majority of patients, an intervention will do more good than harm
- ‘Do not offer’ – the intervention will not be of benefit for most patients

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- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

LETR (Linking evidence to recommendations) statements

As clinical guidelines were previously formatted, there was limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' and will usually cover the following key points:

- the relative value placed on the outcomes considered
- the strength of evidence about benefits and harms for the intervention being considered
- the costs and cost-effectiveness of an intervention
- the quality of the evidence (see GRADE)
- the degree of consensus within the GDG
- other considerations – for example equalities issues

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed.

Consultation and validation of the guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (Appendix F) had one opportunity to comment on the draft guideline which was posted on the NICE website between 3 September 2014 and 15 October 2014 in line with NICE methodology (NICE 2012).

The pre-publication process

An embargoed pre-publication version of the guideline was released to registered stakeholders to allow them to see how their comments have contributed to the development of the guideline and to give them time to prepare for publication (NICE 2012).

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other versions of the guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc)/

NICE also produces three other versions of the bladder cancer guideline which are available from the NICE website:

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- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations
- NICE pathways, which is an online tool for health and social care professionals that brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.
- 'Information for the Public (IFP)', which summarises the recommendations in the guideline in everyday language for patients, their family and carers, and the wider public.

Updating the guideline

Literature searches were repeated for all of the clinical questions at the end of the guideline development process, allowing any relevant papers published before 6 June 2014 to be considered. Future guideline updates will consider evidence published after this cut-off date.

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

Funding

The National Collaborating Centre for Cancer was commissioned by NICE to develop this guideline.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

References

National Institute for Health and Clinical Excellence (2012) The guidelines manual. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidelinesmanual

Whiting P, Rutjes A. Reitsma J, Bossuyt P & Kleijnen J (2003) The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology, 3: 25.

Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM, Group Q-2 (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine, 155: 529-536.

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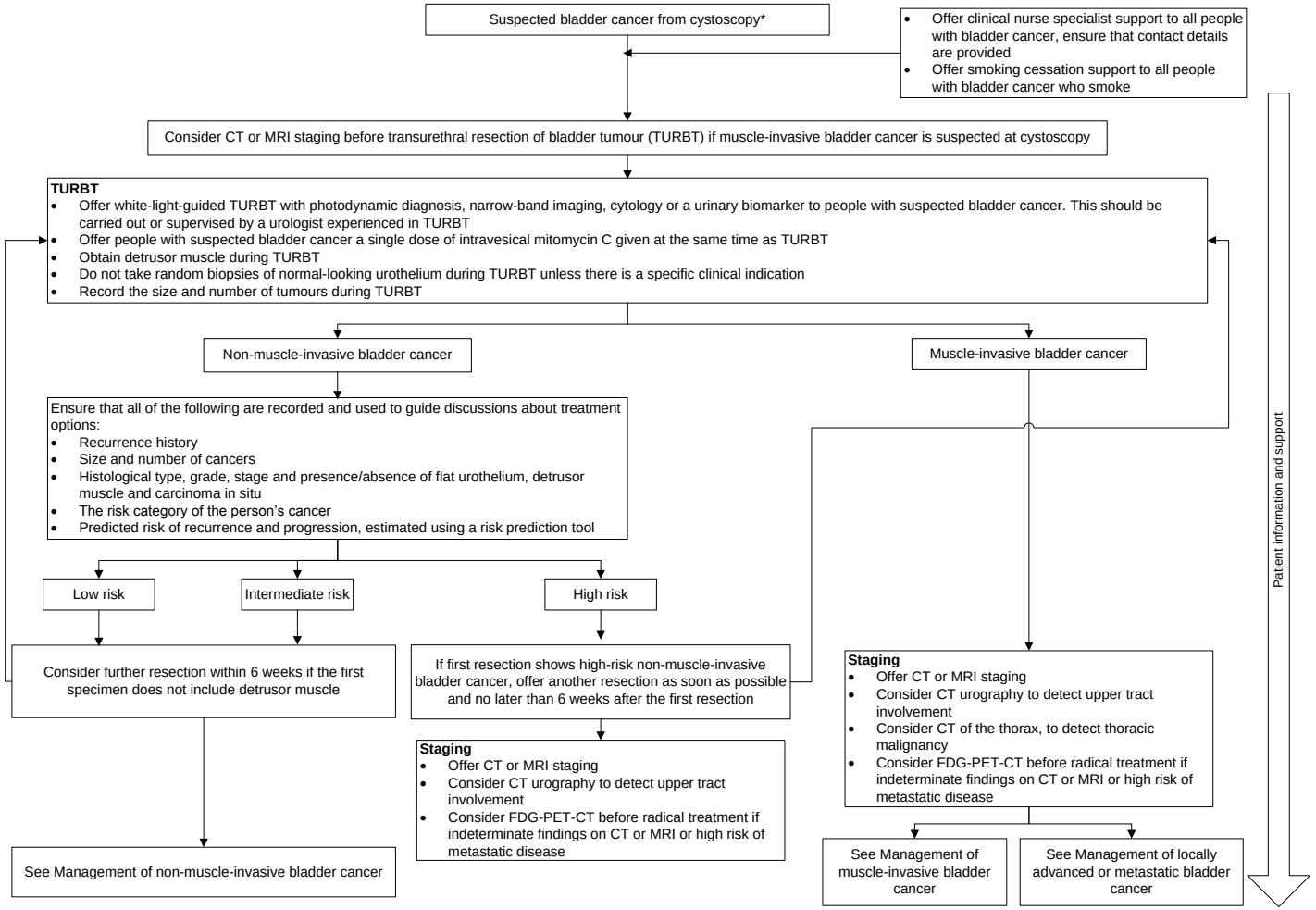
Algorithms

Diagnosis and staging



*Do not substitute urinary biomarkers for cystoscopy to investigate suspected bladder cancer or for follow-up after treatment for bladder cancer, except in the context of a clinical research study

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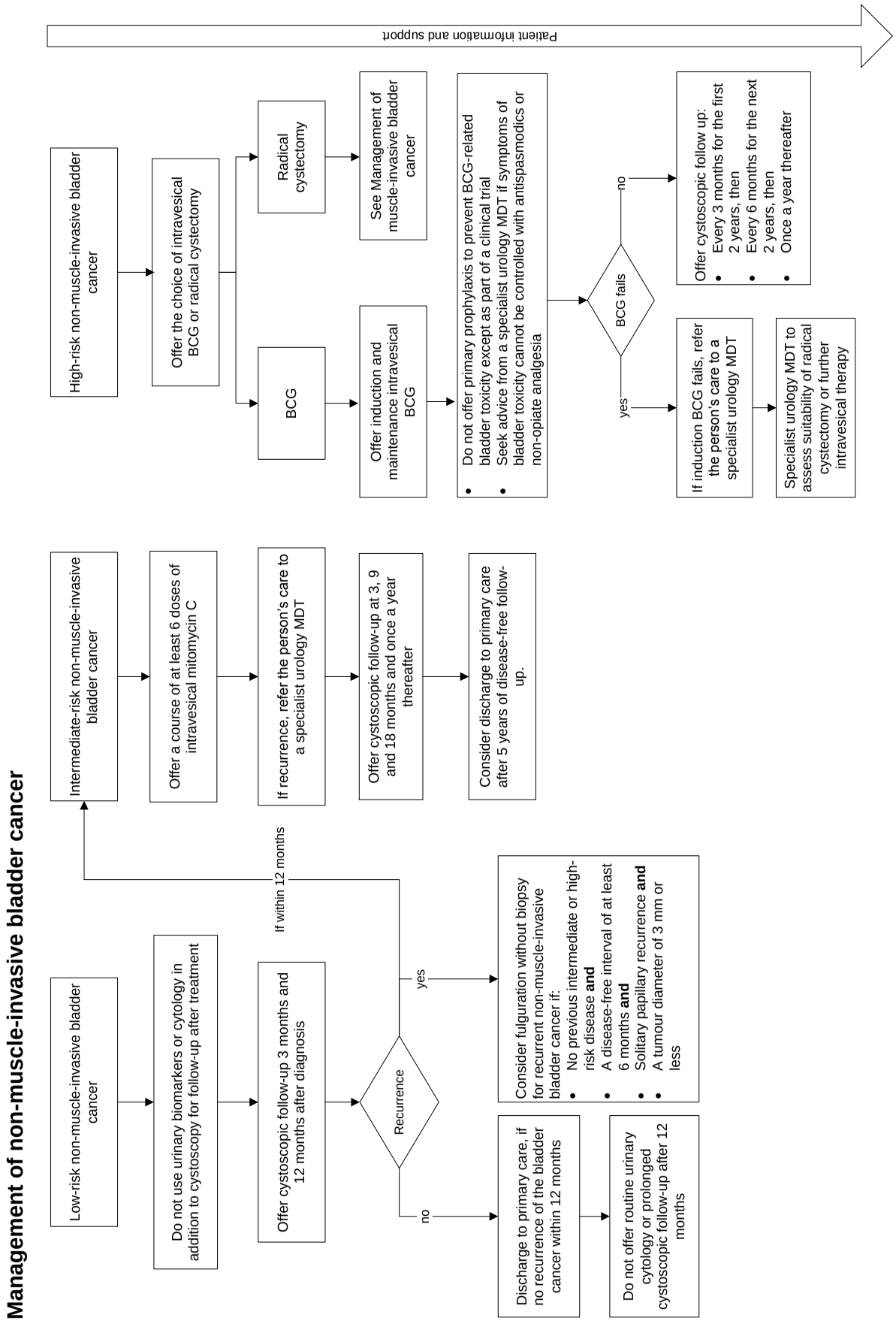

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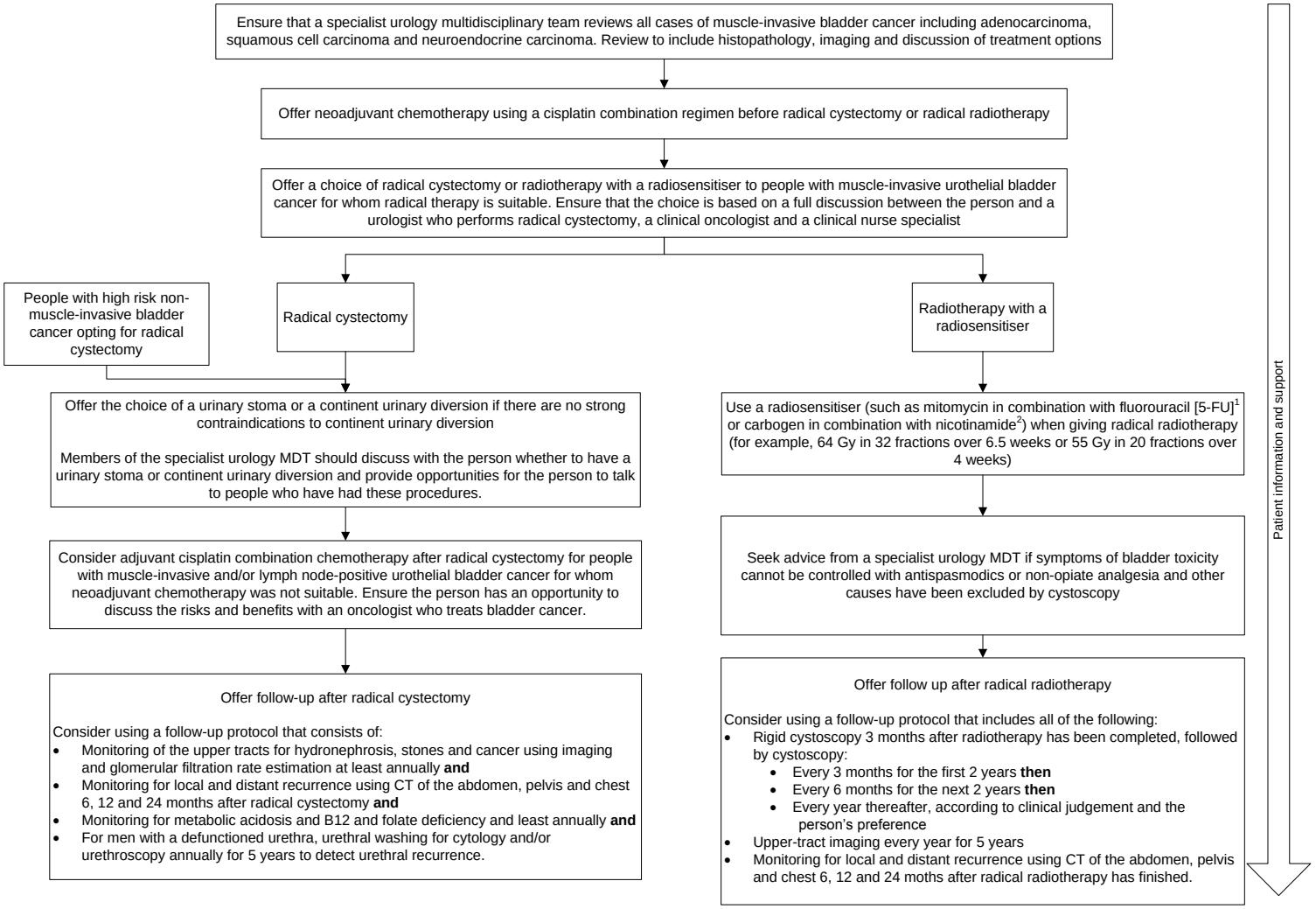
Management of muscle-invasive bladder cancer



[1] At the time of publication (February 2015) neither mitomycin or [5-FU] had a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicinesfor further information.

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

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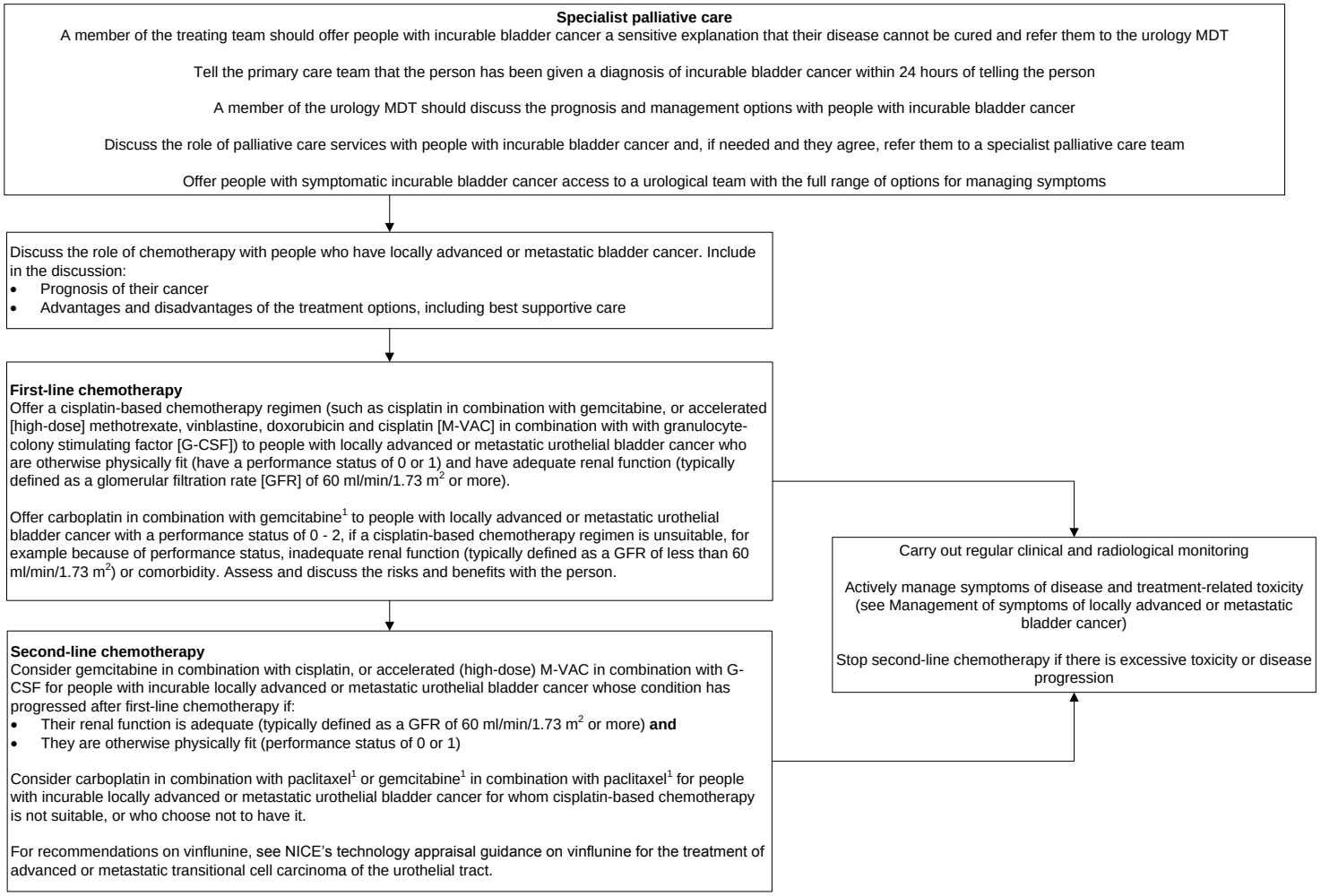
Management of locally advanced or metastatic bladder cancer



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

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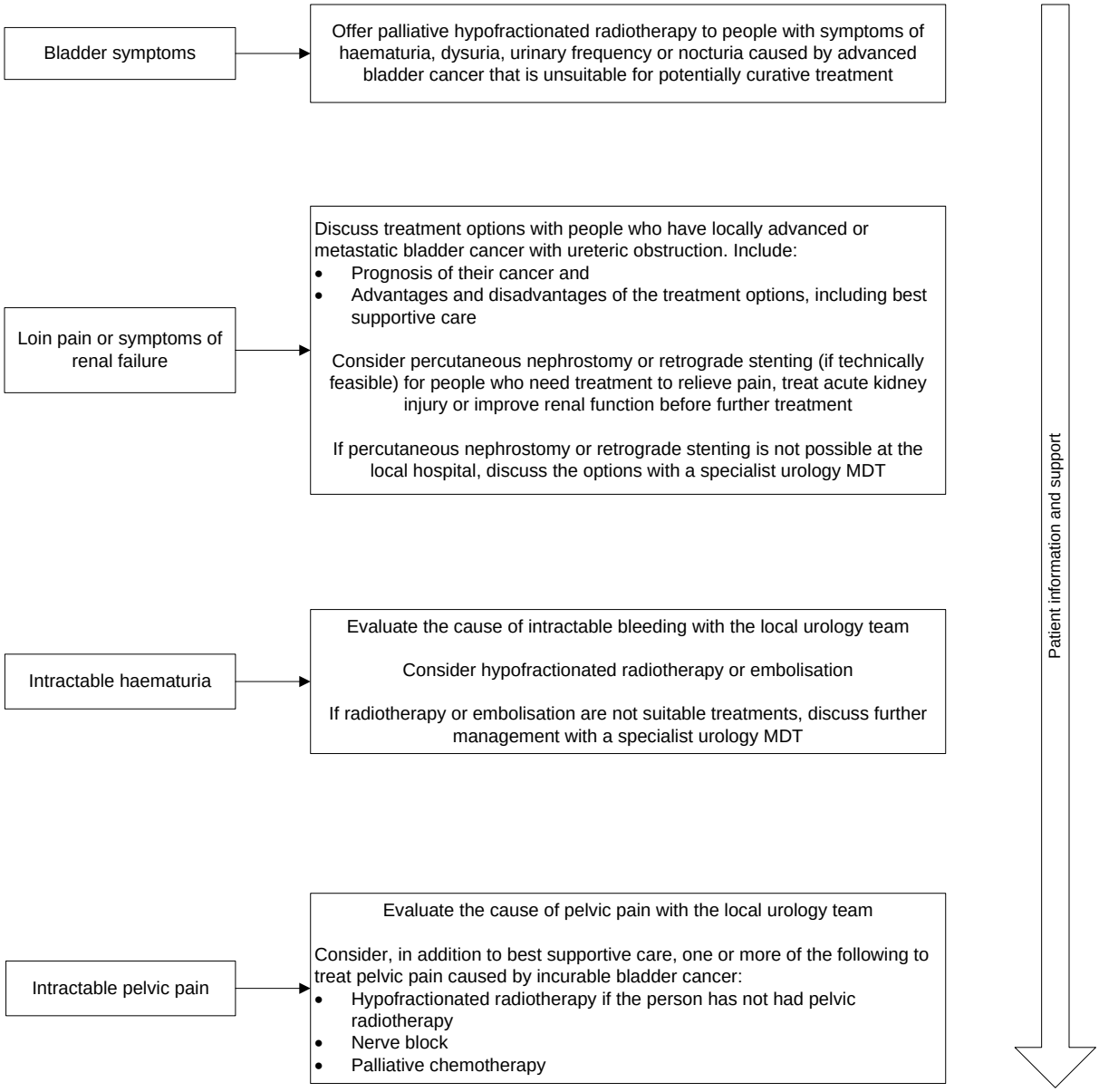
Managing symptoms of locally advanced or metastatic bladder cancer



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1 Epidemiology

Bladder cancer is the seventh most common cancer in the UK, with just over 10,000 cases diagnosed each year (CRUK, 2013a). These are unevenly split between men (fourth most common cancer) and women (11th most common cancer).

Around 5,000 people each year die from bladder cancer, making it the seventh most common cause of cancer death (CRUK, 2013b). As with new diagnoses these are unevenly split between men (sixth most common cancer death) and women (12th most common cancer death).

There are a number of well-known risk factors for bladder cancer, with the main risk being increasing age. Smoking is also a key risk and the chance of developing bladder cancer is about three times higher in smokers (Parkin, 2011a). There are also certain industrial chemicals linked to bladder cancer: these chemicals are now controlled but it is estimated they account for about 7% of males and 2% of female bladder cancers (Parkin, 2011b).

1.1 Methods

Incident cases were extracted from the National Cancer Registration Service (NCRS) in England, and the Welsh Cancer Intelligence and Surveillance Unit (WCISU) in Wales. The following codes were used to identify cases:

- C67 'Malignant neoplasm of bladder'
- D09.0 'Carcinoma in situ of bladder '
- D41.4 'Neoplasm uncertain/unknown behaviour of bladder'

All deaths in England and Wales are certified by a medical professional and then processed by the Office for National Statistics (ONS). The ONS derive a single underlying cause of death which is used to identify bladder cancer deaths.

Deprivation in England has been measured using the income deprivation component of the English Indices of Deprivation (DCLG, 2012). In Wales the Welsh Index of Multiple Deprivation (WIMD) is used (Welsh Government, 2014).

1.2 Incidence

It is only valid to analyse data from the year 2000 onwards for England, and 2007 onwards for Wales. This is due to a change of coding.

Since 2000 the age-standardised rate (ASR) in men in England has decreased by 1.7% each year on average, and the ASR in women has decreased by 1.3% each year. The ASR in men is over three times that in women: 17.8 per 100,000 in men and 5.3 per 100,000 in women. In 2012 6,457 men in England were diagnosed with bladder cancer, compared to 2,453 women (Figure 1).

In Wales, since 2007, the ASR in men has decreased by an average of 4.1% each year. The ASR in 2012 was 16.8 per 100,000 in men and 5.6 per 100,000 in women. In 2012 393 men in Wales were diagnosed with bladder cancer, compared to 160 women (Figure 2).

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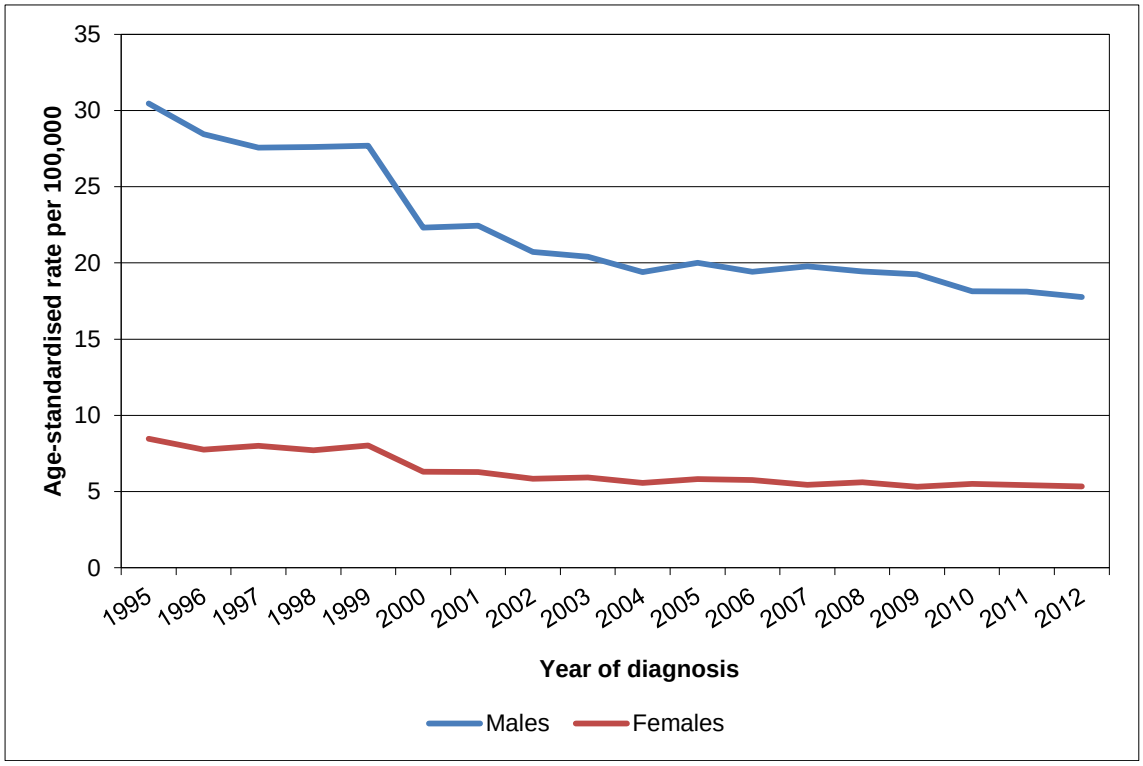
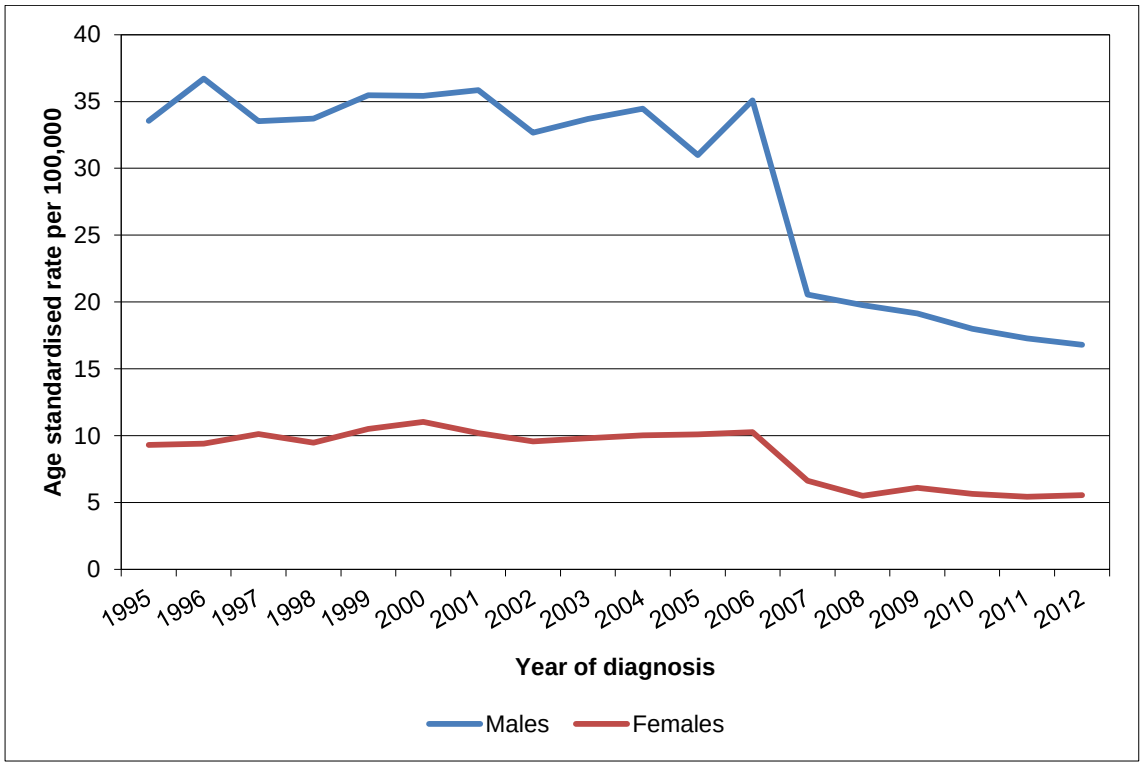
Figure 1: Incidence of bladder cancer (ICD-10 code C67), age-standardised rate per 100,000 by sex, England 1995-2012.



Source: NCRS; ONS

Figure 2: Incidence of bladder cancer (ICD-10 code C67), age-standardised rate per 100,000 by sex, Wales 1995-2012.



Source: WCISU; ONS

The majority of bladder cancers are urothelial carcinoma but there are differences by sex. In both England and Wales urothelial carcinomas are more common in men ($p<0.001$ for both)

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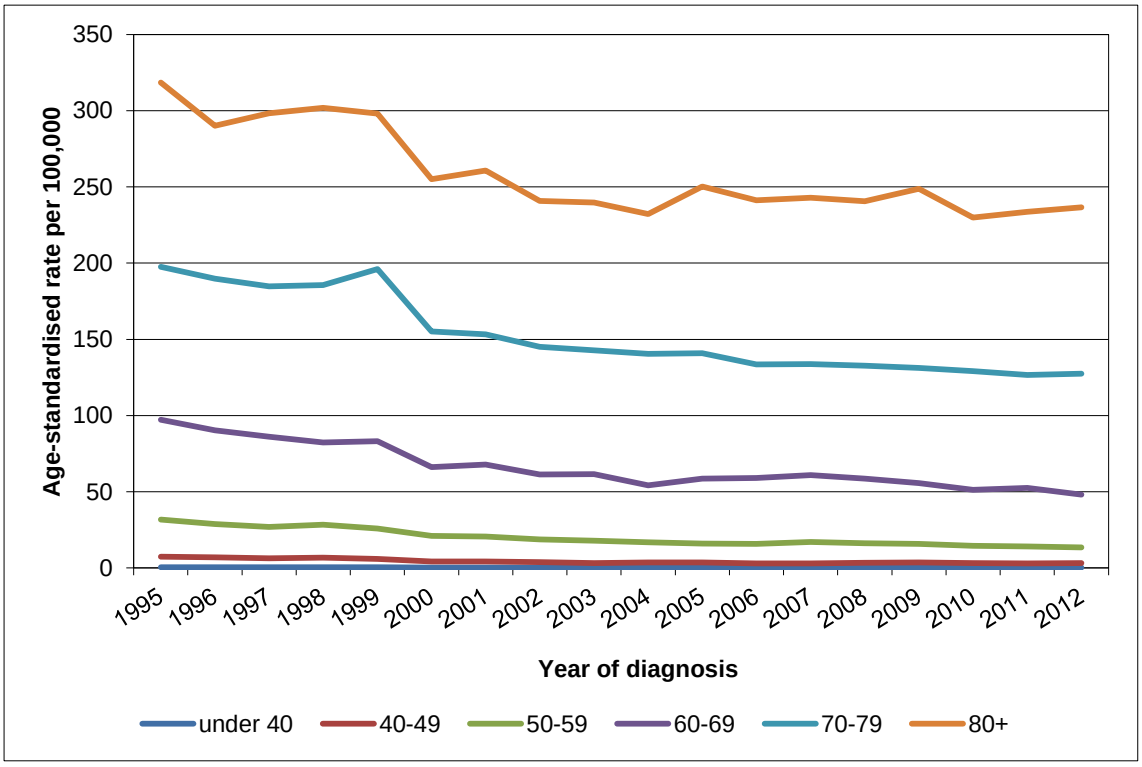
and squamous cell cancers more common in women (p<0.001 for both). In England sarcomas are more common in women (p=0.003), however there are very few cases so the magnitude of the difference is small.

The rate of bladder cancer incidence increases with age in both males and females, with the highest rates occurring in those aged 80 and over (Figures 3 and 4). In England in 2012 34% of cases in men were diagnosed in those aged 80+ (2,200 cases) and 43% of cases in women were diagnosed in those aged 80+ (1,048 cases). This proportion has increased steadily since the year 2000, when 25% of cases in men and 38% of cases in women were in those aged 80 and over. This is likely to be a result of an aging population, but also a cohort effect of those who may have been exposed via industry in the 1950s/60s or had higher smoking prevalence (Figures 3 and 4).

In Wales the highest age-specific rates are also in those aged 80 and over. In 2012 31% of cases in men were diagnosed in those aged 80+ (123 cases) and 40% of cases in women were diagnosed in those aged 80+ (64 cases). This proportion is largely unchanged since 2007 (Figures 5 and 6).

Figure 3: Incidence of bladder cancer (ICD-10 code C67) in men, age-specific rate per 100,000, England 1995-2012.



Source: NCRS; ONS

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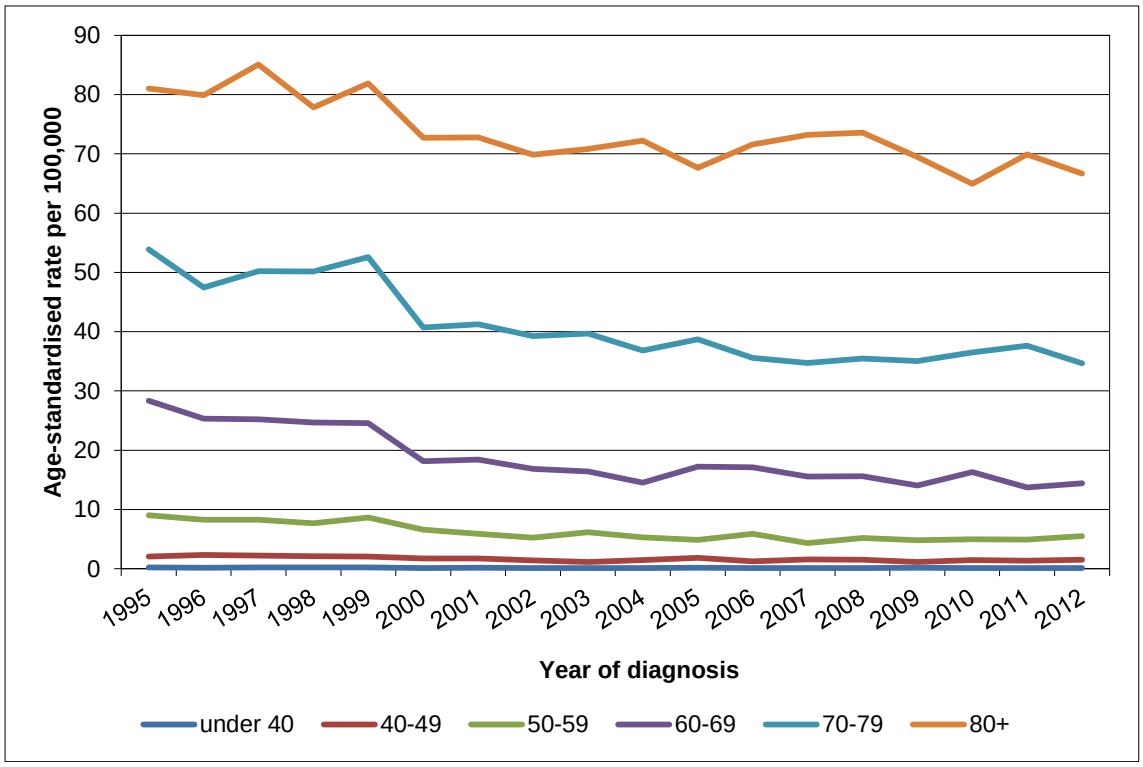
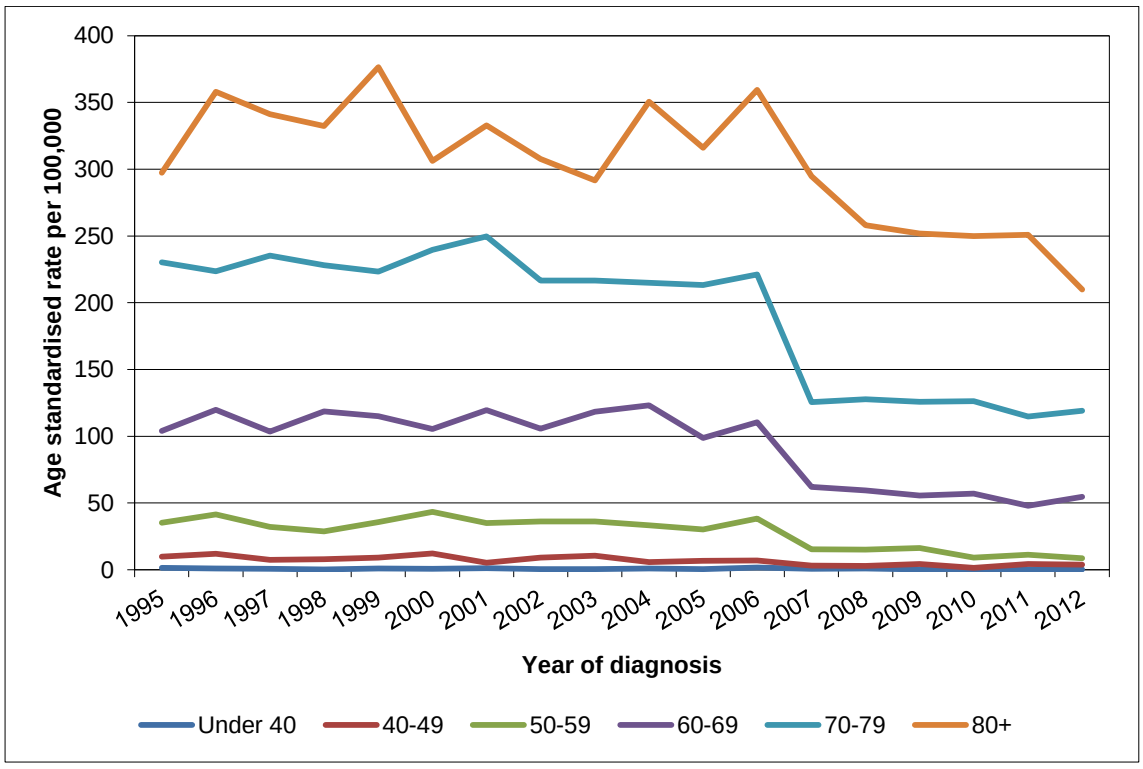
Figure 4: Incidence of bladder cancer (ICD-10 code C67) in women, age-specific rate per 100,000, England 1995-2012.



Source: NCRS; ONS

Figure 5: Incidence of bladder cancer (ICD-10 code C67) in men, age-specific rate per 100,000, Wales 1995-2012.



Source: WCISU; ONS

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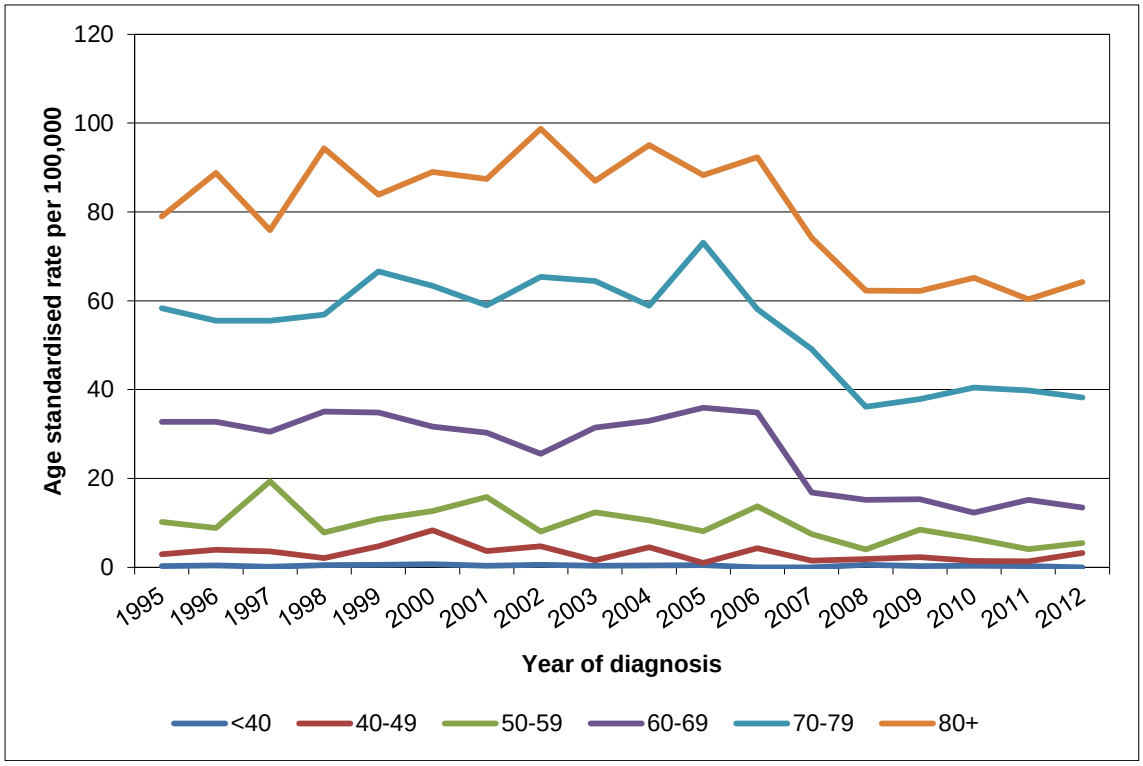
Figure 6: Incidence of bladder cancer (ICD-10 code C67) in women, age-specific rate per 100,000, Wales 1995-2012.



Source: WCISU; ONS

The incidence of bladder cancer in England is higher in the most deprived population compared to the least deprived population ($p<0.001$).

Analysis of trends in data for England indicate that incidence of bladder cancer is decreasing more quickly in the least deprived populations. Therefore the inequality between least and most deprived is growing (Figures 7 and 8).

The numbers of cases in each deprivation quintile in Wales is small, and there are fewer years available for analysis. Therefore we cannot be sure of any trends by deprivation quintile, or if rates are truly higher in the most deprived areas (Figure 9 and 10).

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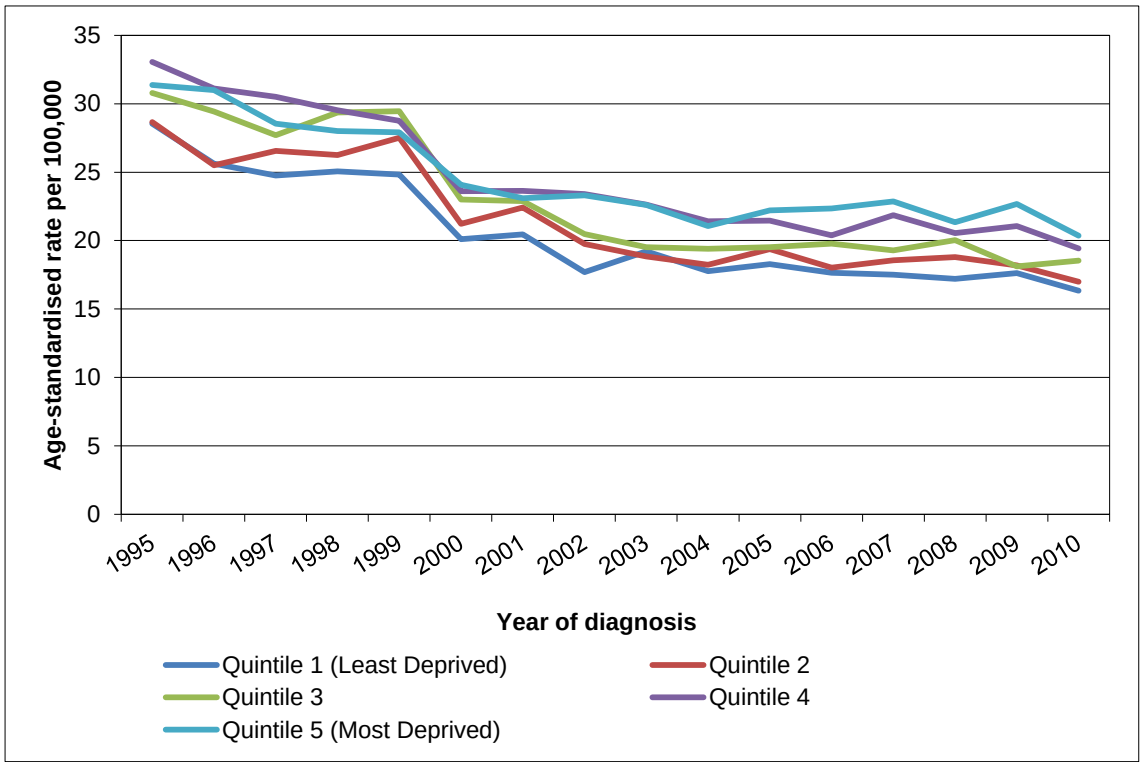
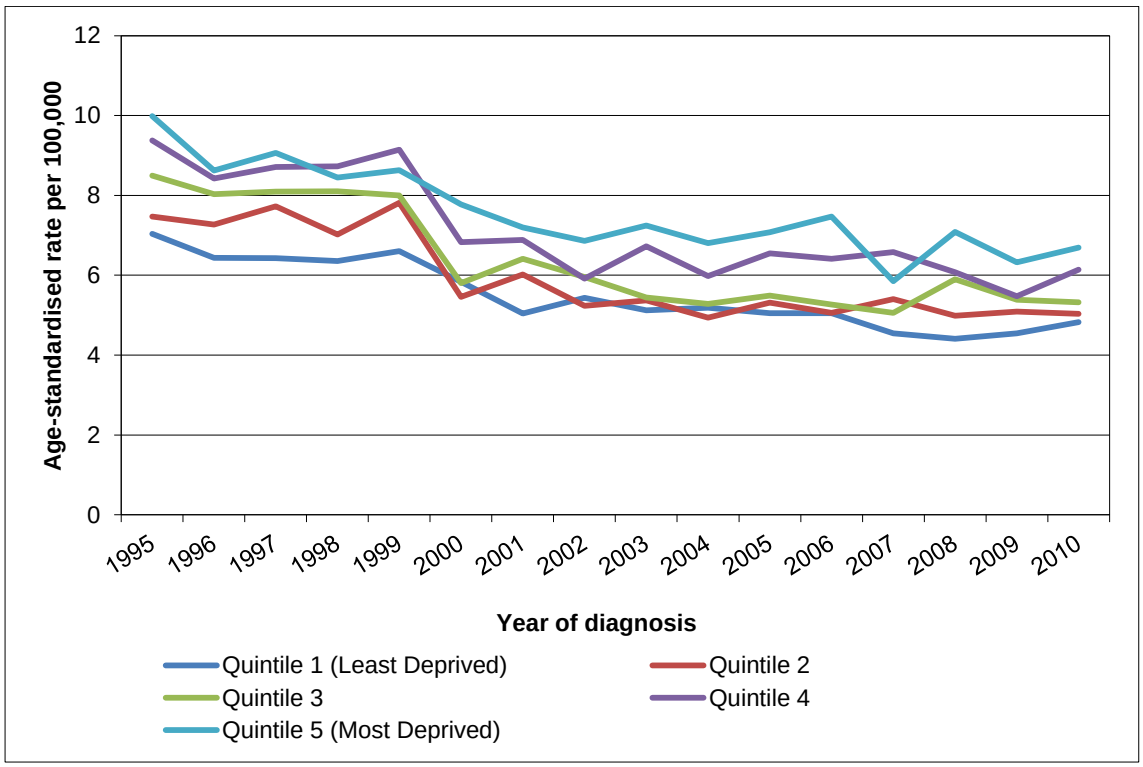
Figure 7: Incidence of bladder cancer (ICD-10 code C67) in men, age-standardised rate per 100,000 by deprivation quintile, England 1995-2010.



Source: NCRS; ONS; DCLG

Figure 8: Incidence of bladder cancer (ICD-10 code C67) in women, age-standardised rate per 100,000 by deprivation quintile, England 1995-2010.



Source: NCRS; ONS; DCLG

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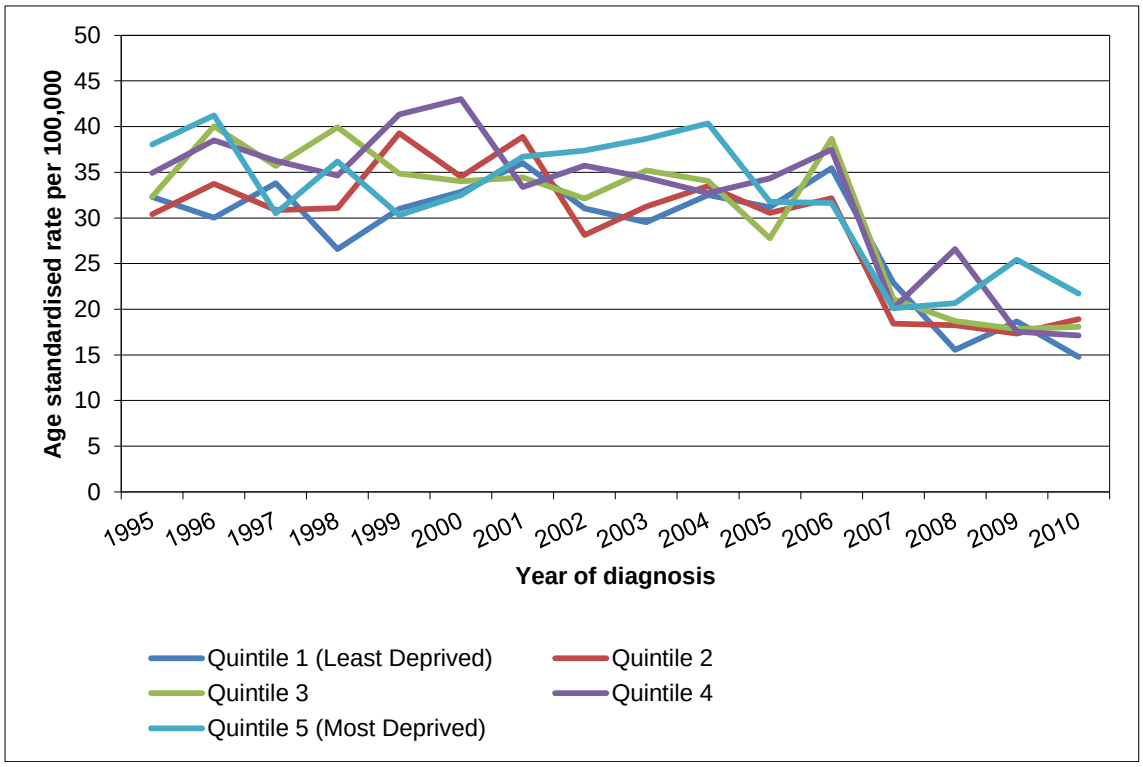
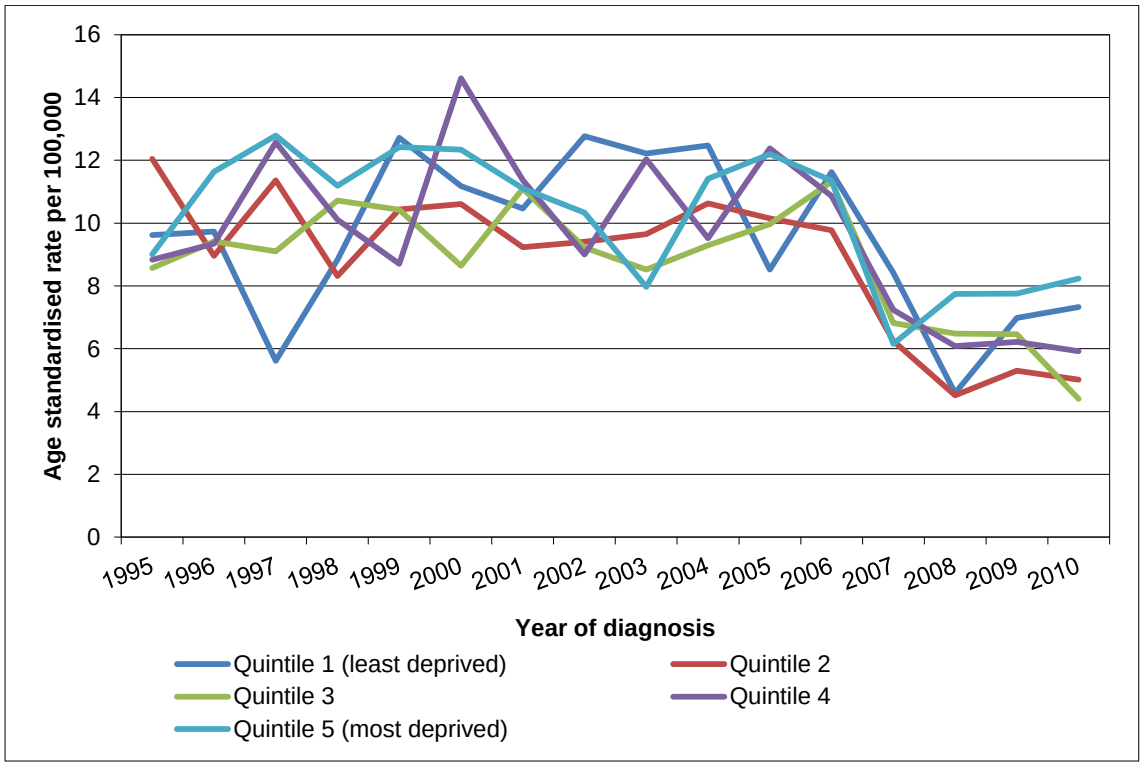
Figure 9: Incidence of bladder cancer (ICD-10 code C67) in men, age-standardised rate per 100,000 by deprivation quintile, Wales 1995-2010.



Source: WCSIU; ONS

Figure 10: Incidence of bladder cancer (ICD-10 code C67) in women, age-standardised rate per 100,000 by deprivation quintile, Wales 1995-2010.



Source: WCSIU; ONS

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Stage at diagnosis is not recorded in all cases. In England in 2012, 35% of diagnoses had a valid TNM stage recorded. Of these 34% were stage I, 29% stage II, 6% stage III and 30% stage IV. Recording is better in Wales, with 78% of cases in 2012 having a valid TNM stage. Of these cases, 46% were stage I, 34% stage II, 12% stage III and 9% stage IV.

Stage at diagnosis is related to sex, age and deprivation. A logistic regression analysis on data in England and Wales indicates that the greatest difference in odds for being diagnosed with more advanced cancer is between men and women. Women have between 15% and 45% higher odds of advanced disease depending on the country and whether non-malignant bladder tumours (D41.4, D09.0) are included in analysis. Increasing age decreases the odds of being diagnosed with both MIBC and stage IV disease when considering bladder cancer (C67) diagnoses alone. Whilst there is some interaction with deprivation, the magnitude of the change in odds is generally small compared to the effect of sex or age. Increasing age decreases the odds of being diagnosed with both MIBC and stage IV disease when considering bladder cancer (C67) diagnoses alone. When all bladder tumours (C67, D41.4, D09.0) are included in the analysis the odds of being diagnosed with MIBC increases with age, however the odds of stage IV disease continue to be lower with increasing age.

Analysis of data at Clinical Commissioning Group (CCG) or Health Board level shows that CCGs with higher than average rates are located in all areas of the country but there is a distinct group around Liverpool, Manchester and Leeds. London has a number of CCGs with lower than average ASRs, plus there are several areas in the Midlands (Figures 11 and 12).

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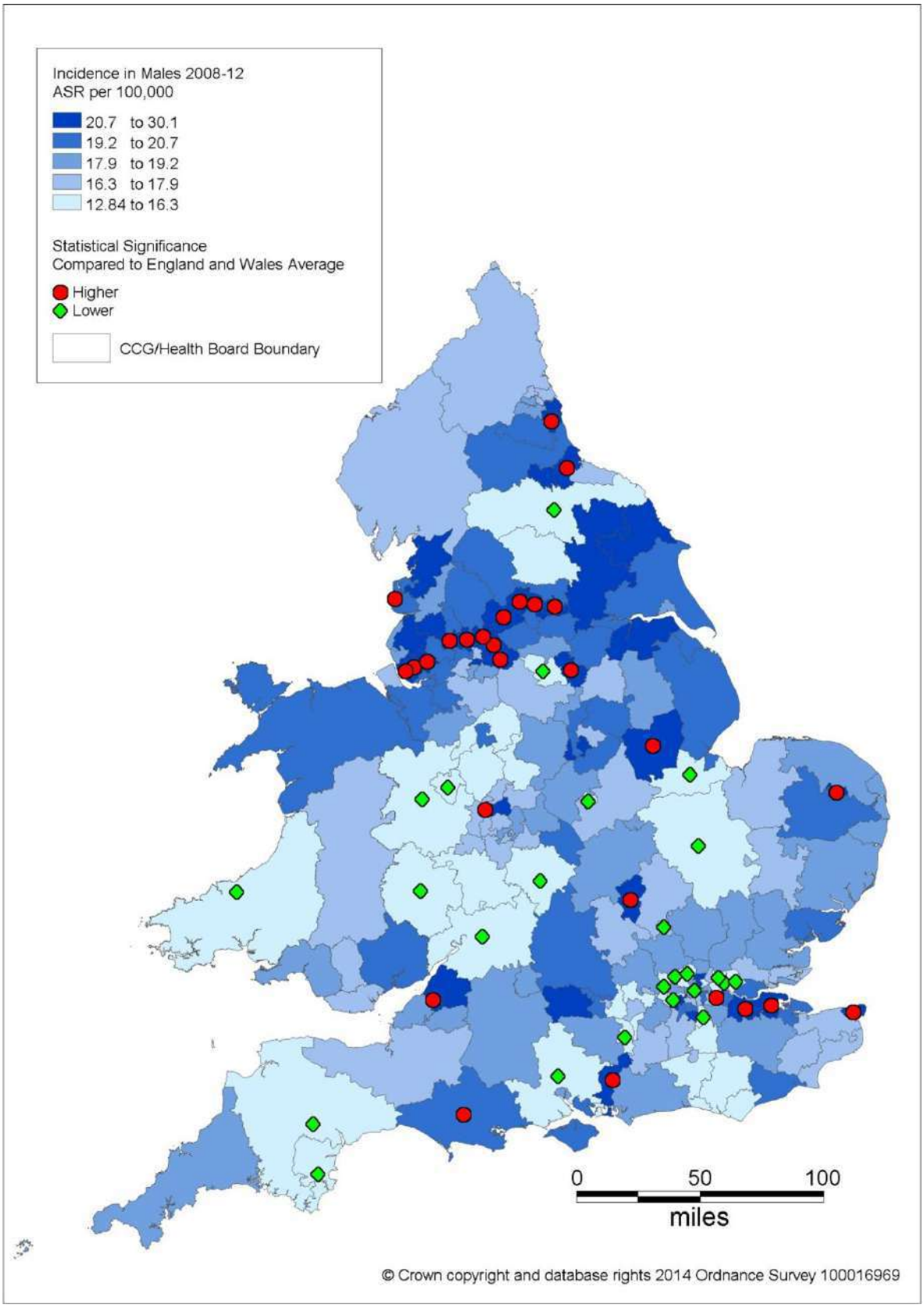
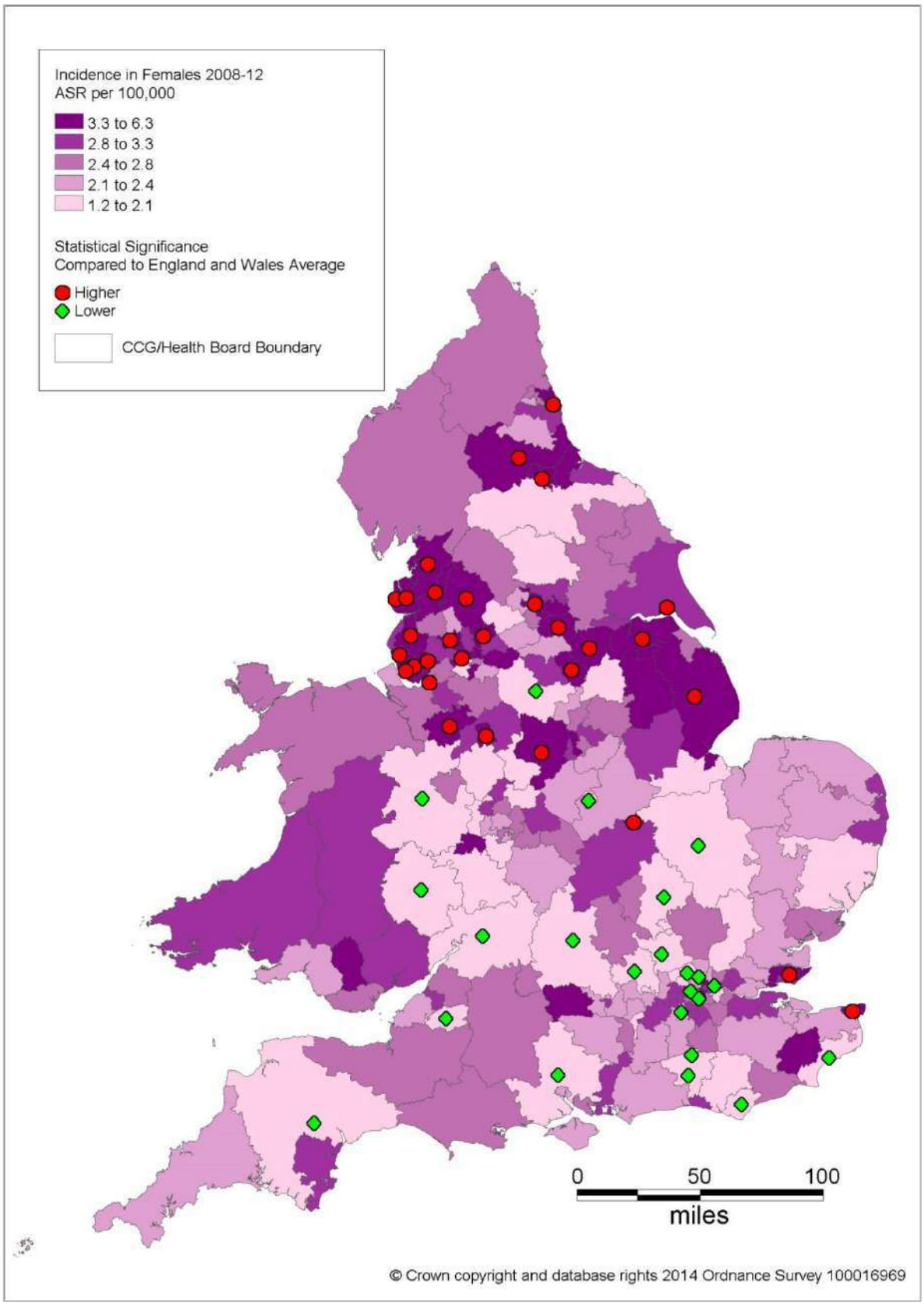
Figure 11: Incidence of bladder cancer (ICD-10 code C67) in men, age-standardised rate per 100,000, Clinical Commissioning Groups (England) and Health Boards (Wales) 2008-2012.



Source: NCRS; WCSIU; ONS

Figure 12: Incidence of bladder cancer (ICD-10 code C67) in women, age-standardised rate per 100,000, Clinical Commissioning Groups (England) and Health Boards (Wales) 2008-2012.



Source: NCRS; WCSIU; ONS

The National Cancer Intelligence Network (NCIN) ran a project to analyse how cancer patients came to be diagnosed with cancer. This project was called 'Routes to Diagnosis' (NCIN, 2013). 16% of men and 24% of women diagnosed with bladder cancer (C67) in 2006-10 were diagnosed via an emergency route. The proportion of cases diagnosed as an emergency increased with age and deprivation, while the proportion diagnosed via a Two Week Wait referral decreased accordingly.

The same study showed that the one-year relative survival was worst in those diagnosed via an emergency route at 34%. In contrast those diagnosed via a Two Week Wait had a one-year survival of 84%.

1.3 Non-malignant bladder tumours

As with bladder cancer, uncertain behaviour tumours and *carcinoma in situ* are more common in men. In England in 2012 the age-standardised rate of *carcinoma in situ* was 4.8 times higher in men than women ($p<0.001$). The age-standardised rate of uncertain behaviour tumours (papilliary tumours) was 3.3 times higher in men than women ($p<0.001$). In Wales in 2012 the age-standardised rate of *carcinoma in situ* was 7.2 times higher in men than women ($p<0.001$) and the age-standardised rate of uncertain behaviour tumours was 2.9 times higher in men than women ($p<0.001$).

In England there were 1,701 diagnoses of *carcinoma in situ* in men in 2012, and 420 in women. The corresponding number of uncertain behaviour tumours was 4,601 and 1,611. In Wales in 2012 there were 74 diagnoses of *carcinoma in situ* in men and 10 in women, and 319 diagnoses of uncertain behaviour tumours in men and 123 in women.

Between 2000 and 2012 there was no increase or decrease in the ASR of *carcinoma in situ* in either men or women in England. The ASR of uncertain behaviour tumours increased by 3.7% each year in men and by 4.5% each year in women over the same time period. There was no evidence of an increase or decrease in the ASR of *carcinoma in situ* or uncertain behaviour tumour in Wales post 2007.

1.4 Mortality

The code change which affects bladder cancer incidence data in 2000/2007 does not have an effect on deaths data because virtually no people were registered as dying from non-malignant bladder tumours. Therefore it is possible to compare mortality rates over a longer time period.

Deaths from bladder cancer are more common in men – reflective of the higher incidence rates. In 2012, age-standardised mortality rates (ASMRs) were nearly three times higher in men then in women ($p<0.001$). In English men the ASMR was 7.6 per 100,000 and in English women it was 2.8 per 100,000 (Figure 13). In Welsh men the ASMR was 6.8 per 100,000 and in Welsh women it was 2.5 per 100,000 (Figure 14).

In 2012 2,918 men in England died from bladder cancer, compared to 1,399 women. The equivalent figures in 1995 were 3,075 and 1,488. In Wales in 2012 172 men died from bladder cancer compared to 88 women. The equivalent figures in 1995 were 166 and 93.

Although the number of deaths has only varied slightly, the ASMRs have fallen consistently over the time studied. In English men, rates decreased more quickly from 1997 to 2005 (2.5% each year) than from 2005 to 2012 (1.3% per year) (Figure 13). In English women the rate has fallen steadily from 1995 to 2012 at 1.3% each year (Figure 13). In men in Wales the ASMR has decreased steadily at 1.8% from 1995 to 2012, but in women there was not enough evidence to say that the rate has fallen (Figure 14). This will be affected by the smaller number of deaths.

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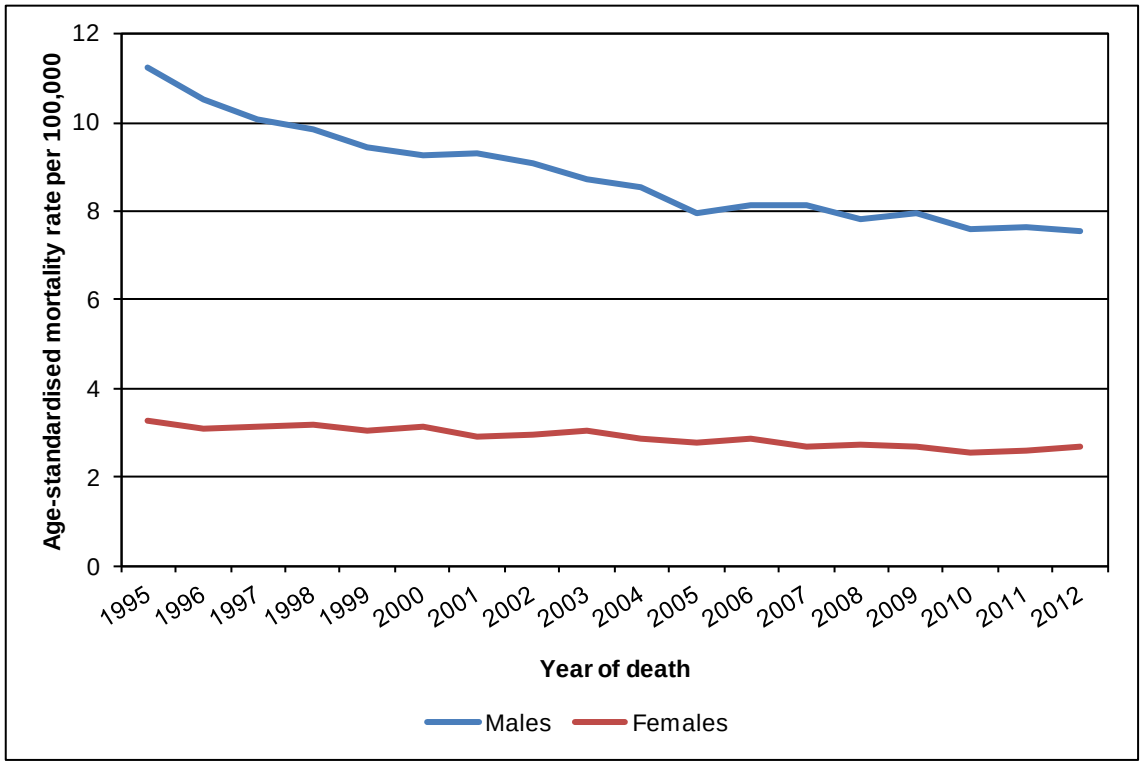
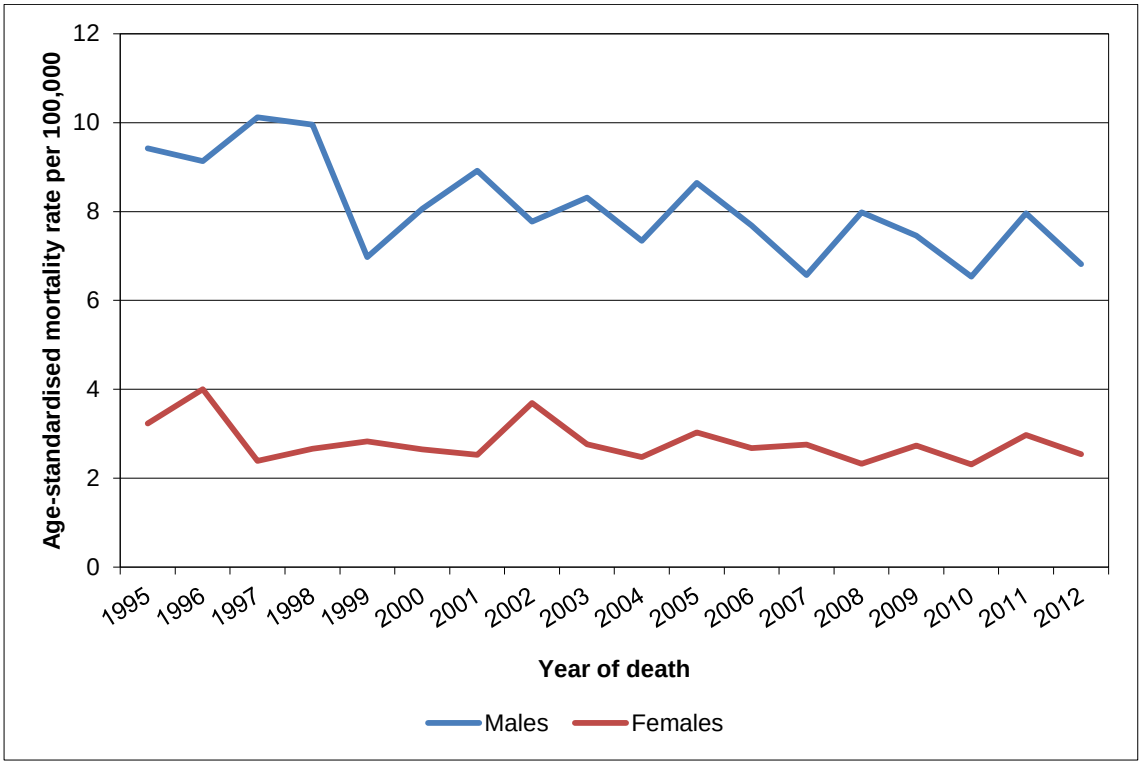
Figure 13: Mortality from bladder cancer (ICD-10 code C67), age-standardised rate per 100,000 by sex, England 1995-2012.



Source: ONS

Figure 14: Mortality from bladder cancer (ICD-10 code C67), age-standardised rate per 100,000 by sex, Wales 1995-2012.



Source: ONS

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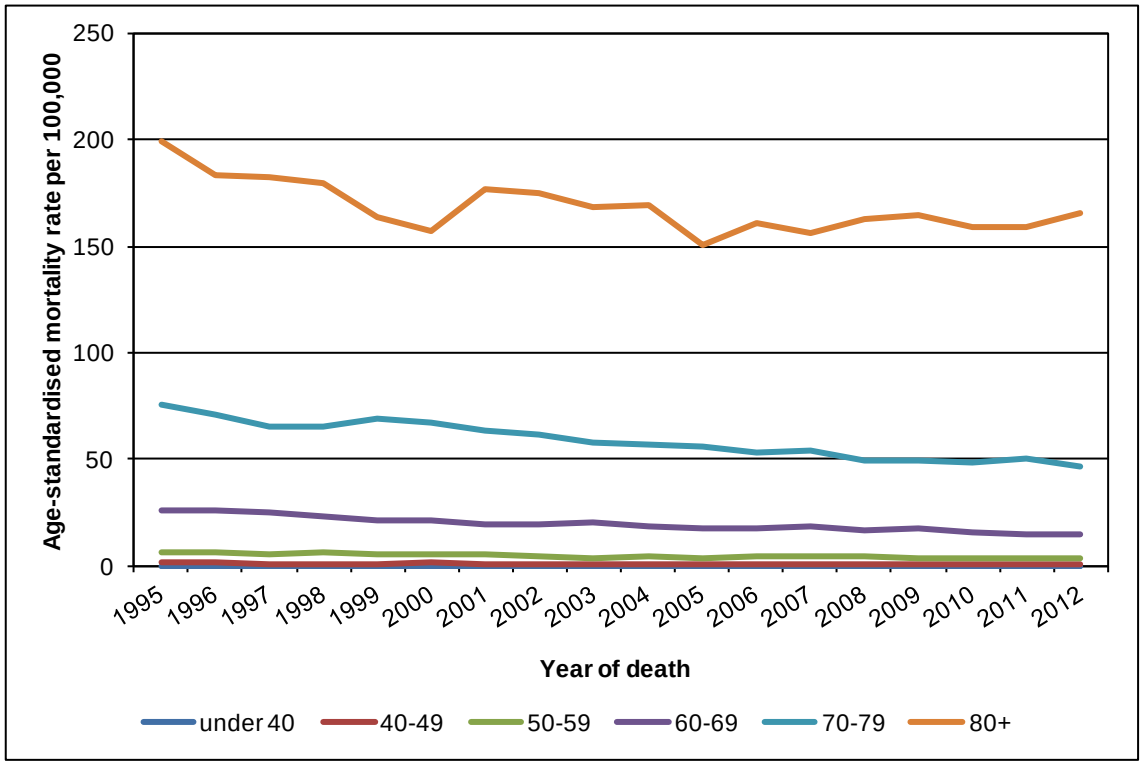
Both the number of deaths and the ASMR is highest in those aged 80 and over. In men the rate in those aged 80 and over is 3.5 times (England) or 4.3 times (Wales) the rate in those aged 70-79. In women it is 2.8 times (England) or 3.3 times (Wales) higher ($p<0.001$ for all) (Figures 15-18).

In men in England, there has been a decreasing trend in age-specific mortality at all ages 40 and over. The largest proportional decrease has been in those men aged 60-69, where the age-specific rate has decreased by 3.3% yearly from 1995 to 2012 (Figure 15). In Welsh men, there is no evidence of a decrease outside ages 60-79. In both men aged 60-69 and men aged 70-79 the rate has steadily decreased by 2.5% each year from 1995 to 2012 (Figure 16).

The number of deaths in women is smaller so there is less power to detect trends in age-specific rates. In England only those women aged 60-69 and 70-79 show statistically significant decreases. In those aged 60-69 the rate has decreased by 2.6% each year from 1995 to 2012, and in those aged 70-79 the rate has decreased by 2.5% each year from 1998 to 2012 (Figure 17). In women in Wales there was a statistically significant decrease only in those aged 60-69, with an annual average decrease of 3.4% from 1995 to 2012 (Figure 18).

Figure 15: Mortality from bladder cancer (ICD-10 code C67) in men, age-specific rate per 100,000, England 1995-2012.



Source: ONS

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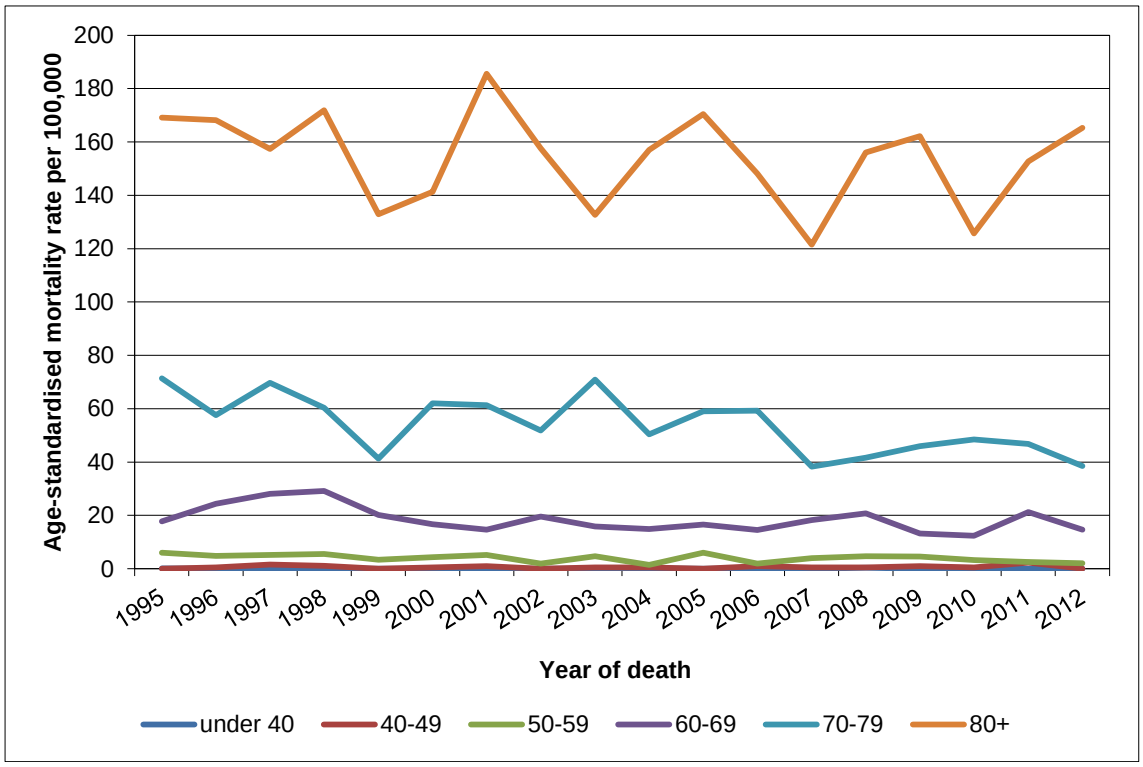
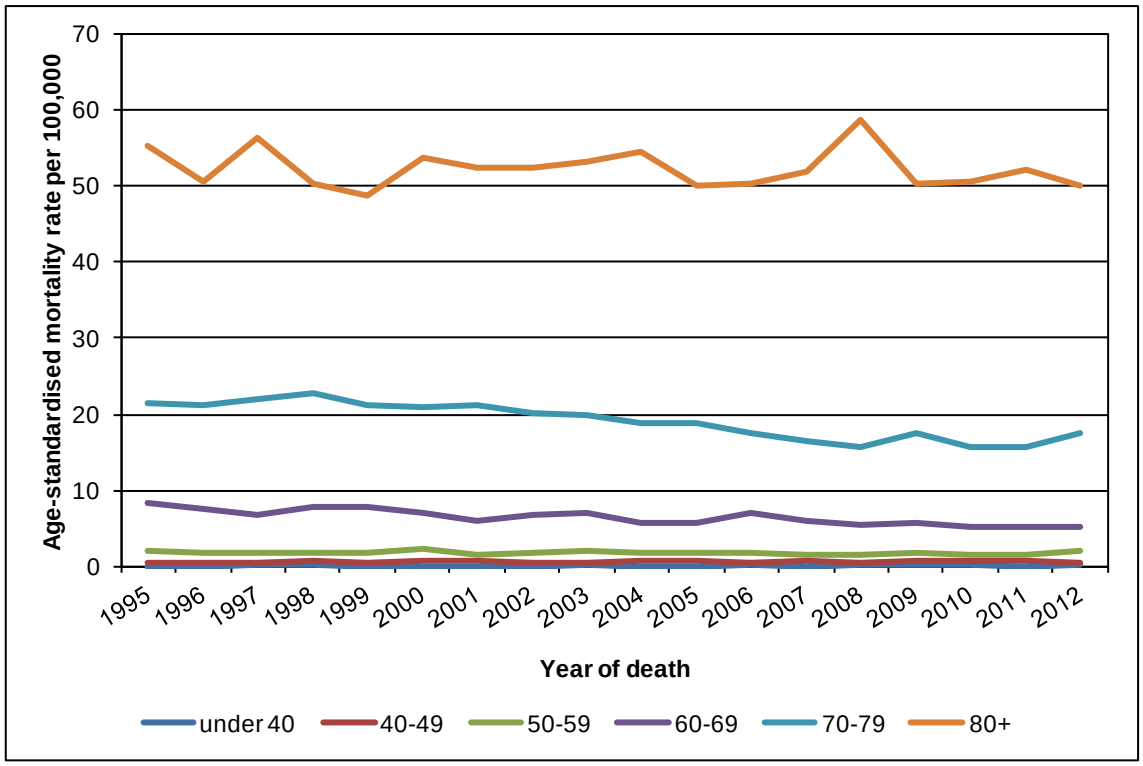
Figure 16: Mortality from bladder cancer (ICD-10 code C67) in men, age-specific rate per 100,000, Wales 1995-2012.



Source: ONS

Figure 17: Mortality from bladder cancer (ICD-10 code C67) in women, age-specific rate per 100,000, England 1995-2012.



Source: ONS

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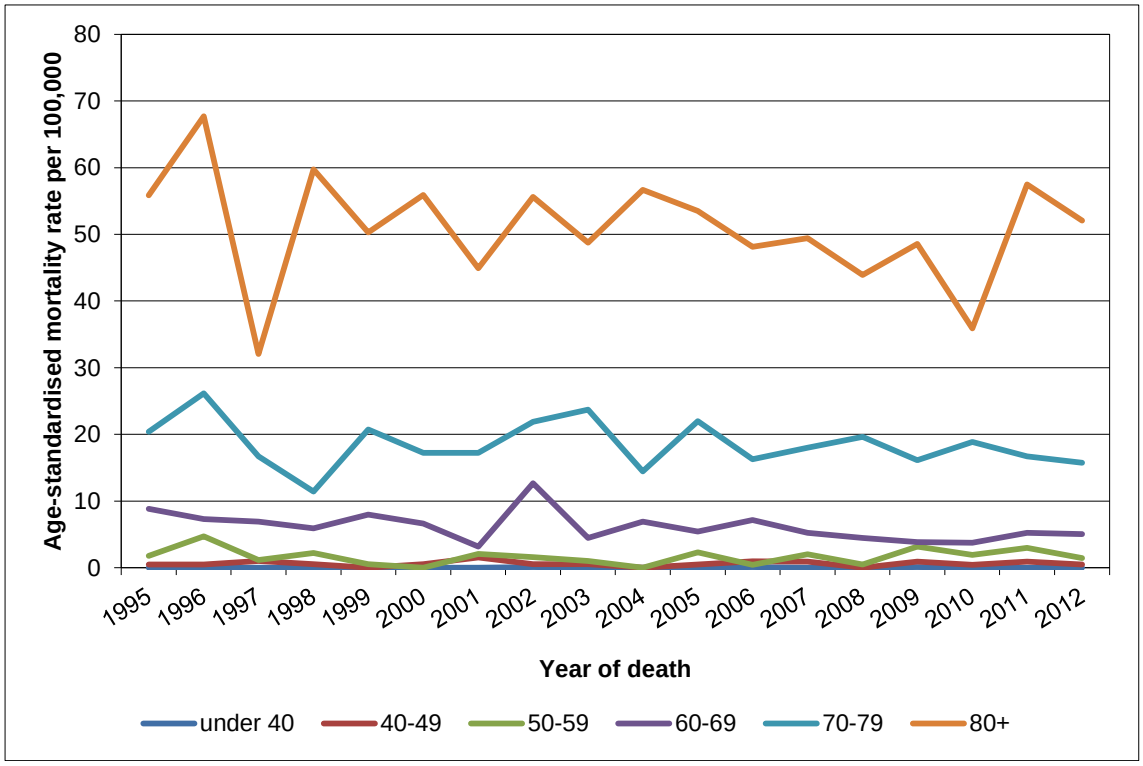
Figure 18: Mortality from bladder cancer (ICD-10 code C67) in women, age-specific rate per 100,000, Wales 1995-2012.



Source: ONS

There is a consistent pattern across England of higher mortality rates in people living in more deprived areas. In 2012 the ASMR in men in the most deprived quintile was 40% higher than in the least deprived; the ASMR in quintile 5 was 9.0 per 100,000 and in quintile 1 was 6.4 per 100,000 ($p<0.001$). In women the ASMR in the most deprived quintile was 65% higher than in the least deprived; the ASMR in quintile 5 was 3.4 per 100,000 and in quintile 1 was 2.0 per 100,000 ($p<0.001$).

In Wales this pattern is not apparent and there is no statistically significant difference between the most and least deprived groups.

ASMRs have fallen in all deprivation groups in England, but there is evidence that the decrease has been larger in the least deprived populations. In men the ASMR in the least deprived quintile decreased by 2.2% each year between 1995 and 2010, compared to 1.1% each year in the most deprived quintile between 1998 and 2010. In women the ASMR in the least deprived quintile decreased by 1.6% each year between 1997 and 2010, compared to 1.1% each year in the most deprived quintile between 1995 and 2010

Those Clinical Commissioning Groups (CCGs) which have a bladder cancer ASMR higher than the England and Wales average tend to be in the north and north-west of England. In contrast the CCGs with lower ASMRs tend to be in the south and south-east of England (Figures 19 and 20).

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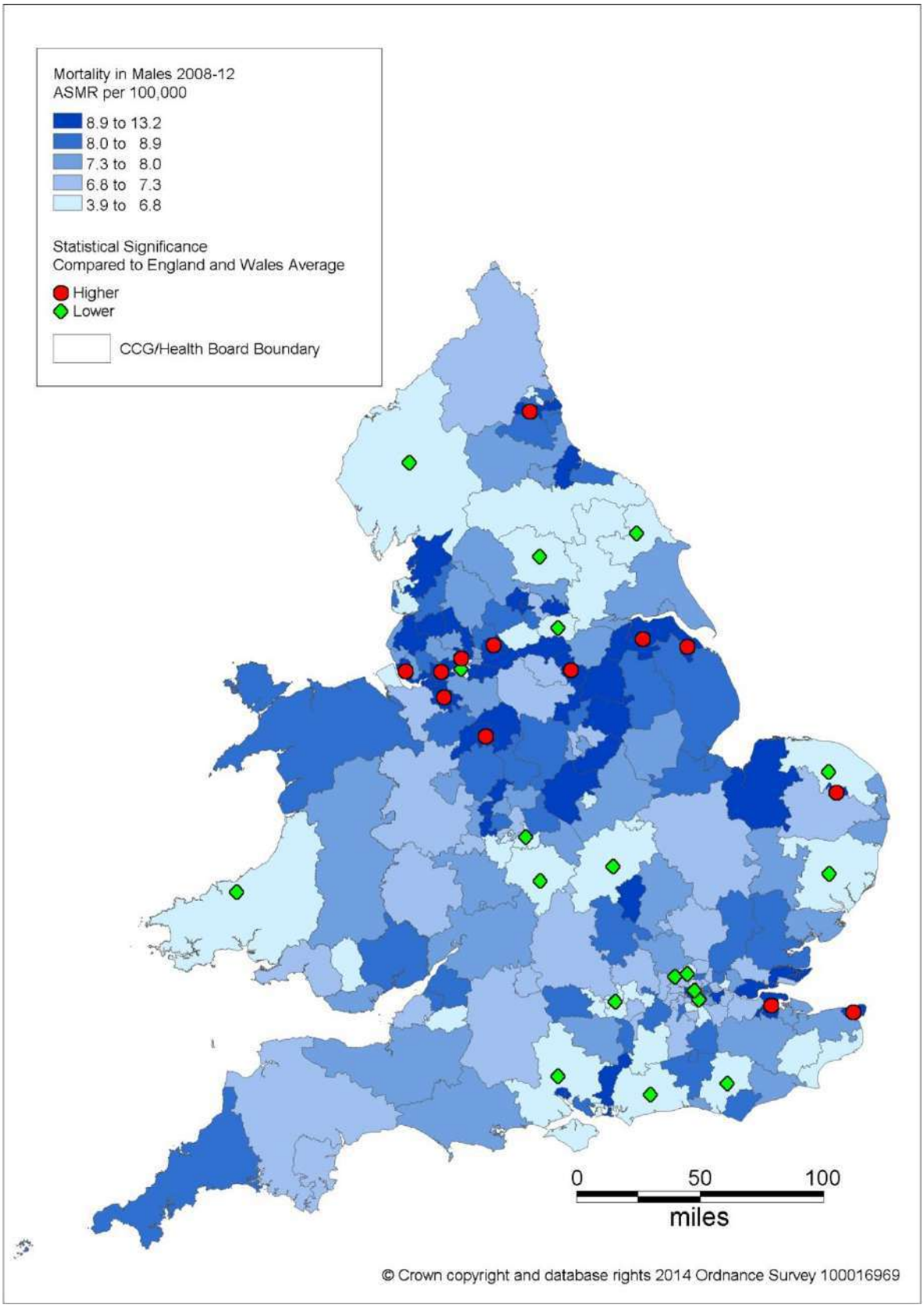
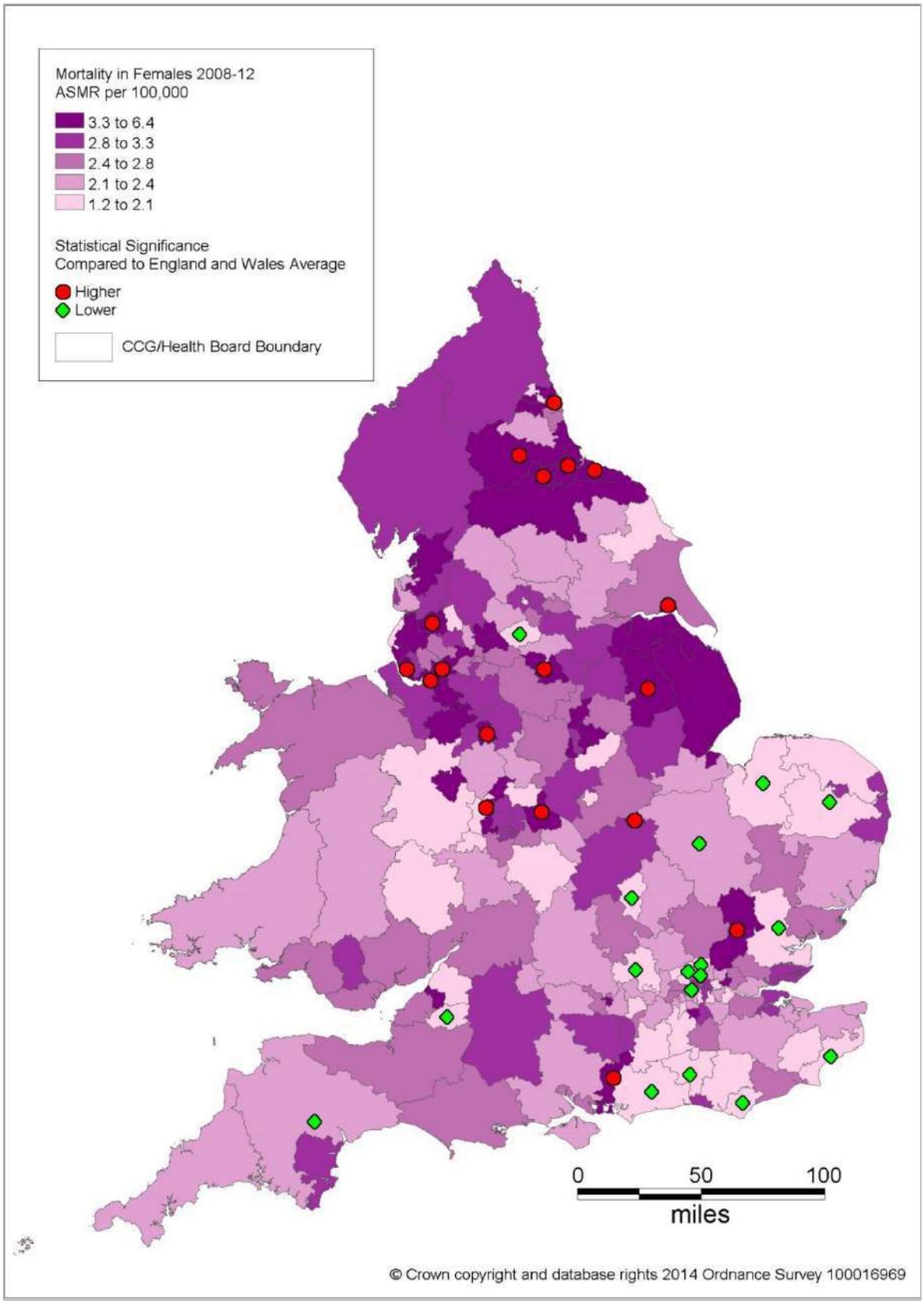
Figure 19: Mortality from bladder cancer (ICD-10 code C67) in men, age-standardised rate per 100,000, Clinical Commissioning Groups (England) and Health Boards (Wales) 2008-2012.



Source: ONS

Figure 20: Mortality from bladder cancer (ICD-10 code C67) in women, age-standardised rate per 100,000, Clinical Commissioning Groups (England) and Health Boards (Wales) 2008-2012.



Source: ONS

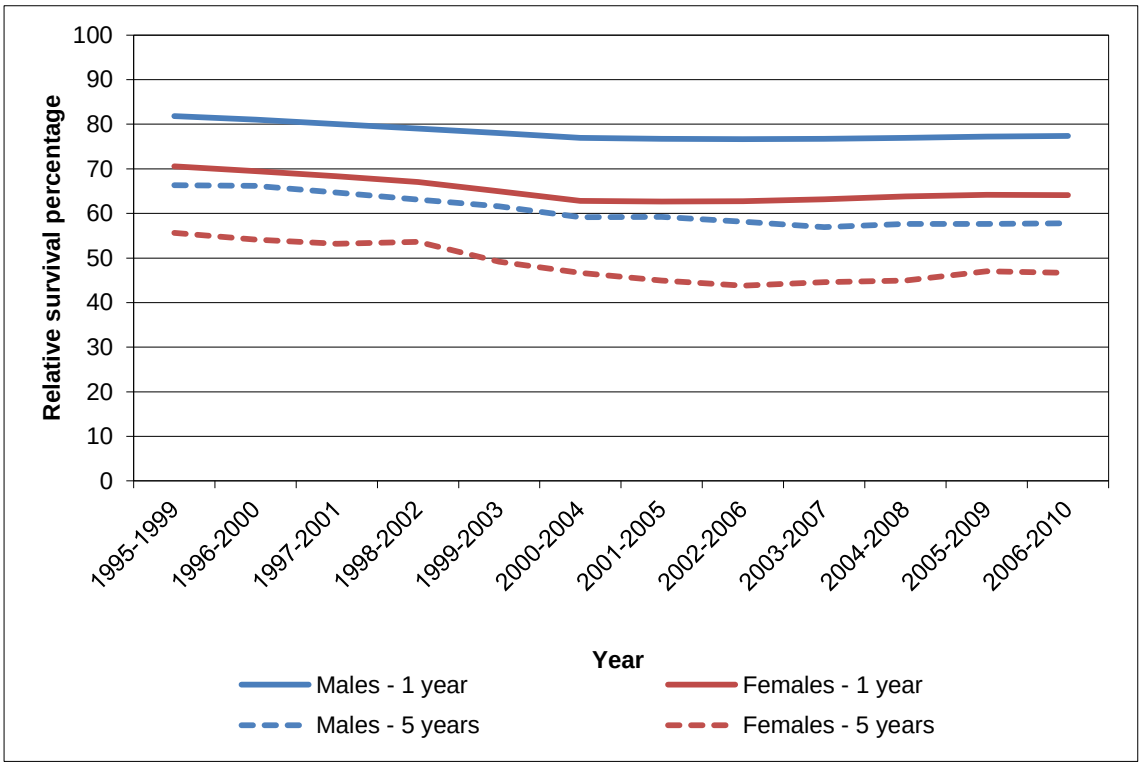
1.5 Survival

Data presented here are for five-year rolling averages as this is necessary for the period survival calculations. Survival data are also affected by the recoding of tumours in the year 2000/2007. As this recoding reduced incidence but had little effect on mortality there was a corresponding reduction in survival. Therefore in England only survival data post-2000 should be assessed. In Wales only one time-period (2007-2011) is after the coding change so no trends can be analysed.

Survival at both one and five years is higher in men than in women; which goes against the general trend for cancer. In England in 2006-10 one-year survival in men was 77% compared to 64% in women. In 2006-10 five-year survival in men was 58% compared to 47% (Figure 21). In Wales in 2007-11 one-year survival in men was 76% compared to 60% in women, and in 2007-11 five-year survival in men was 54% compared to 50% (Figure 22)

In England - for both men and women - there was no difference in survival when comparing 2000-04 and 2006-10, and this is true for all subsequent analysis by separate groups.

Figure 21: Relative survival from bladder cancer (ICD-10 code C67) by sex, England 1995-2010.



Source: NCRS

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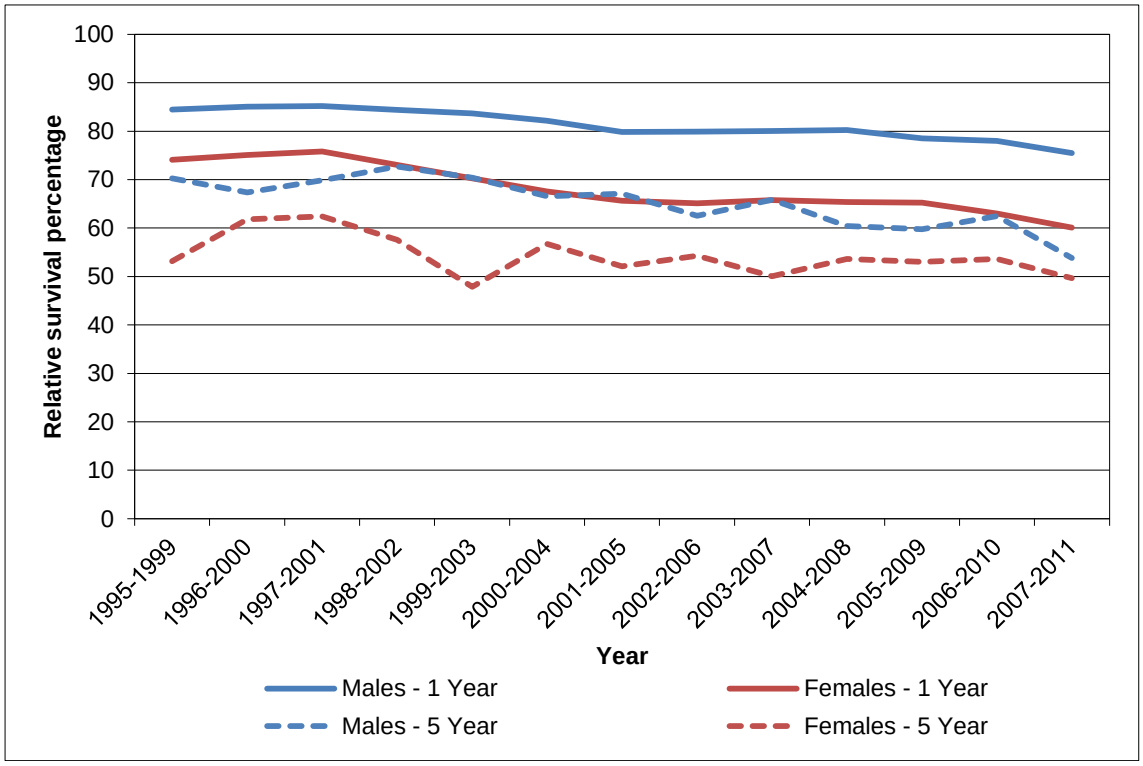
Figure 22: Relative survival from bladder cancer (ICD-10 code C67) by sex, Wales 1995-2011.



Source: WCISU

Survival decreases with age for both men and women, even though relative survival takes into account increased overall mortality rates at older ages. This means that older people have proportionally worse survival as well as worse survival in absolute terms.

In the analysis by age it was not always possible to calculate survival for the youngest patients due to small numbers. This is indicated by gaps in the data.

In men in England in 2006-10 the highest one-year survival was in those aged under 40 at diagnosis at 90%, although the confidence intervals of the four youngest age groups (up to 69 years old) overlap indicating that observed variation is likely to be chance. Survival was worst in those aged 80 and over at diagnosis; where the relative survival was 65% (Figure 23). A similar pattern was seen in women where the one-year survival in under 40s was 77% but 51% in those aged 80 and over (Figure 24).

Five-year survival for men was highest in the under 40s at 76%, compared to 42% in those aged 80 and over. As with one-year survival the rate in those aged under 70 was similar (Figure 25). In women a different pattern is seen, with the highest five-year survival in those aged 50-59 at diagnosis at 61%. The lowest survival was still in the 80+ age group at 32%. The confidence intervals on the youngest age groups overlap all others, likely due to small numbers of diagnoses (Figure 26).

In Wales in 2007-11 one-year survival was highest in men aged under 40, at 87%, As with England data the confidence intervals on this rate overlap all others. Survival in those aged 80 and over is significantly lower than for those aged 50-79, at 60% (Figure 27). For women survival was also lowest in those aged 80 and over and was lower than men of the same age, at 45% (Figure 28).

Five-year survival in Wales is lowest in those aged 80+. In men the rate was 40% and for women the rate was 35% (Figures 29 and 30). This is lower than the rate in 60-69 year olds, but confidence intervals in the oldest ages overlap.

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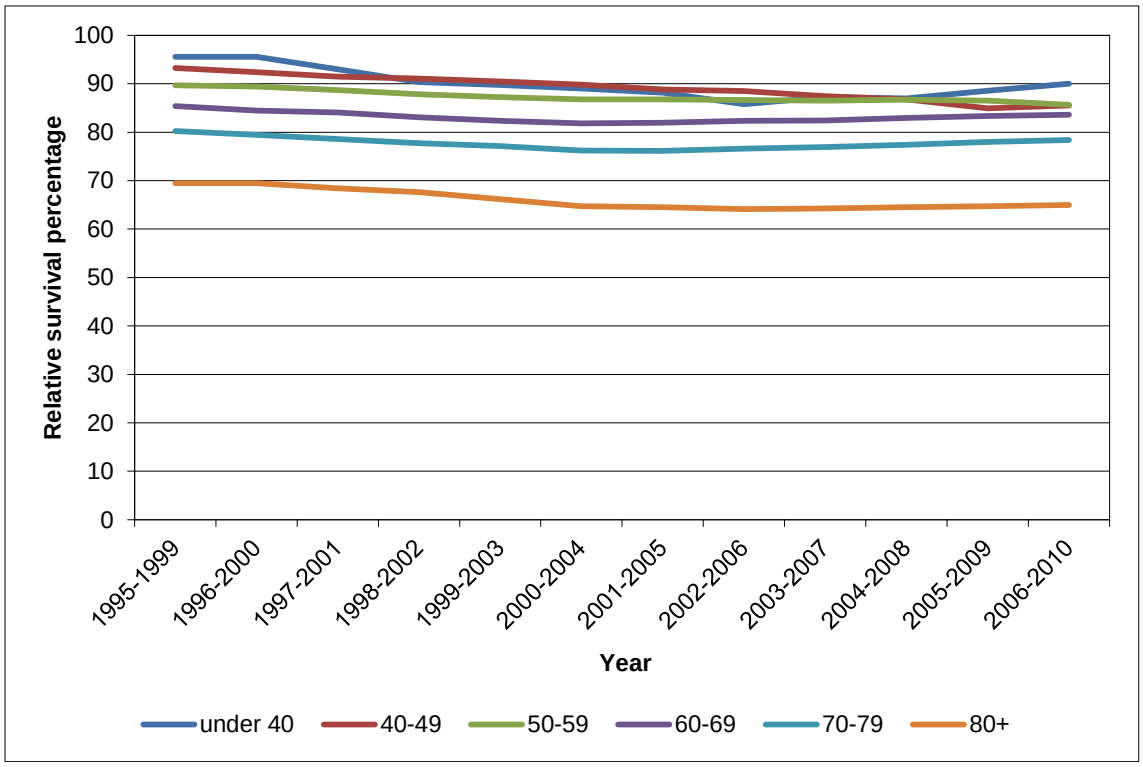
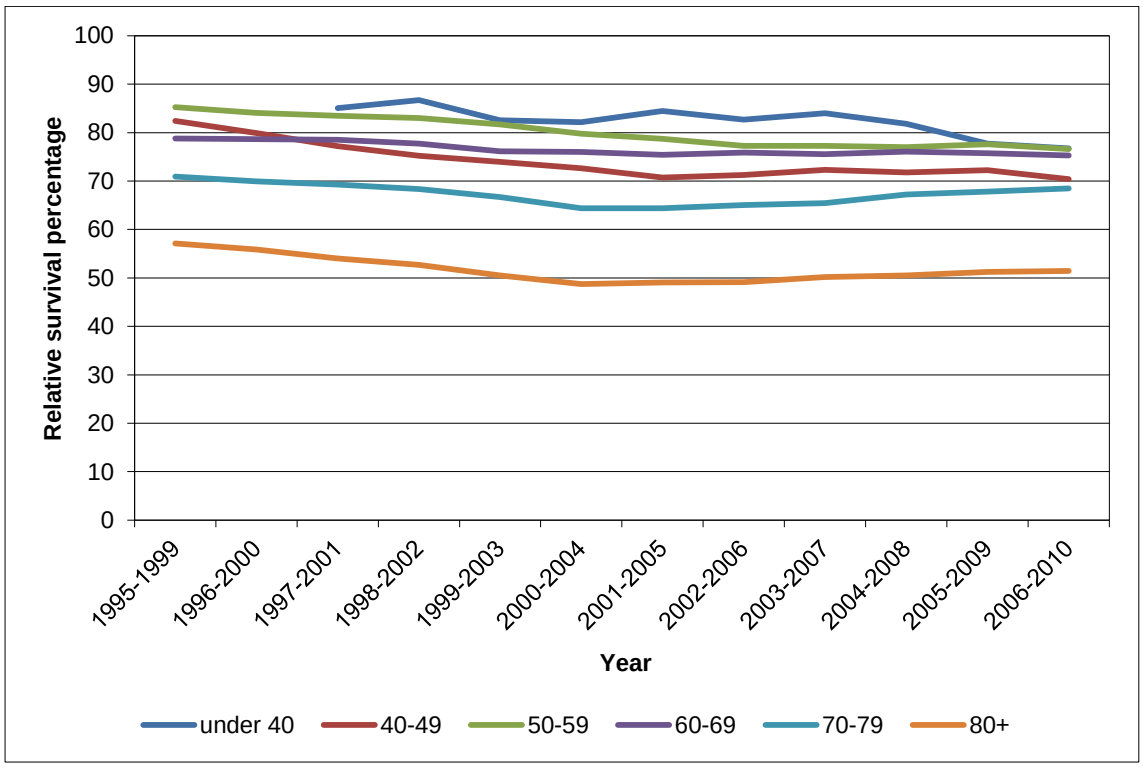
Figure 23: One-year relative survival from bladder cancer (ICD-10 code C67) by age, in men, England 1995-2010.



Source: NCRS

Figure 24: One-year relative survival from bladder cancer (ICD-10 code C67) by age, in women, England 1995-2010.



Source: NCRS

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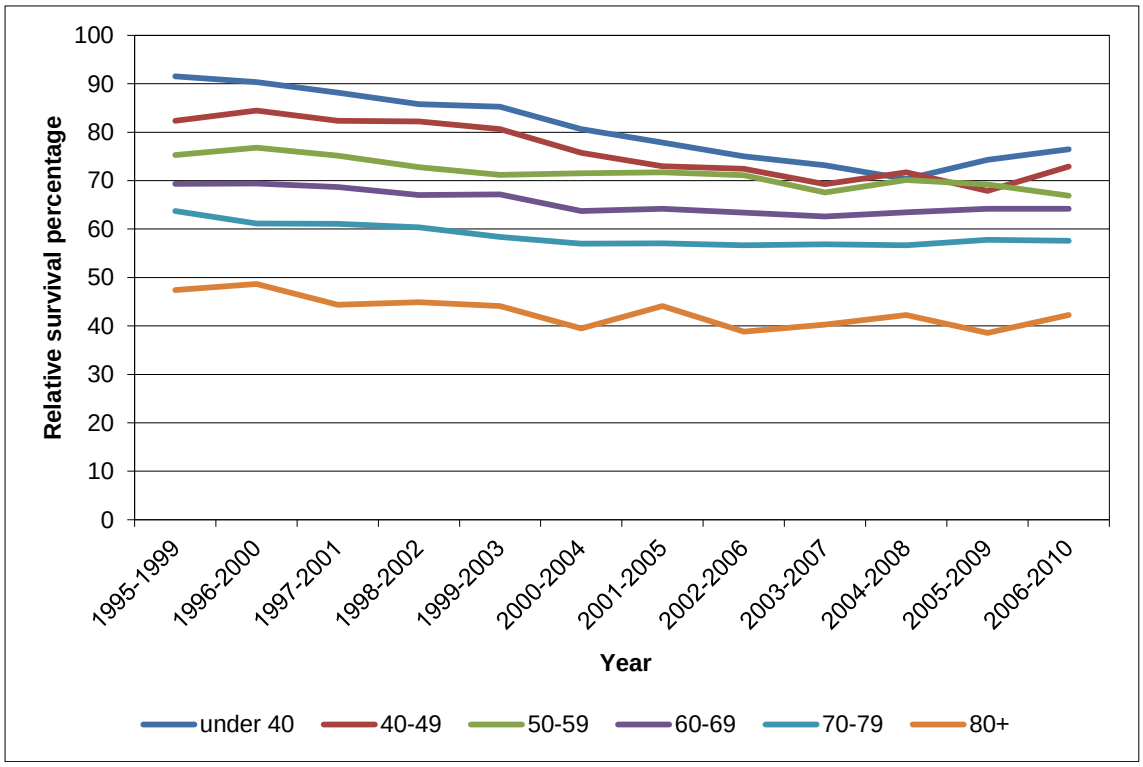
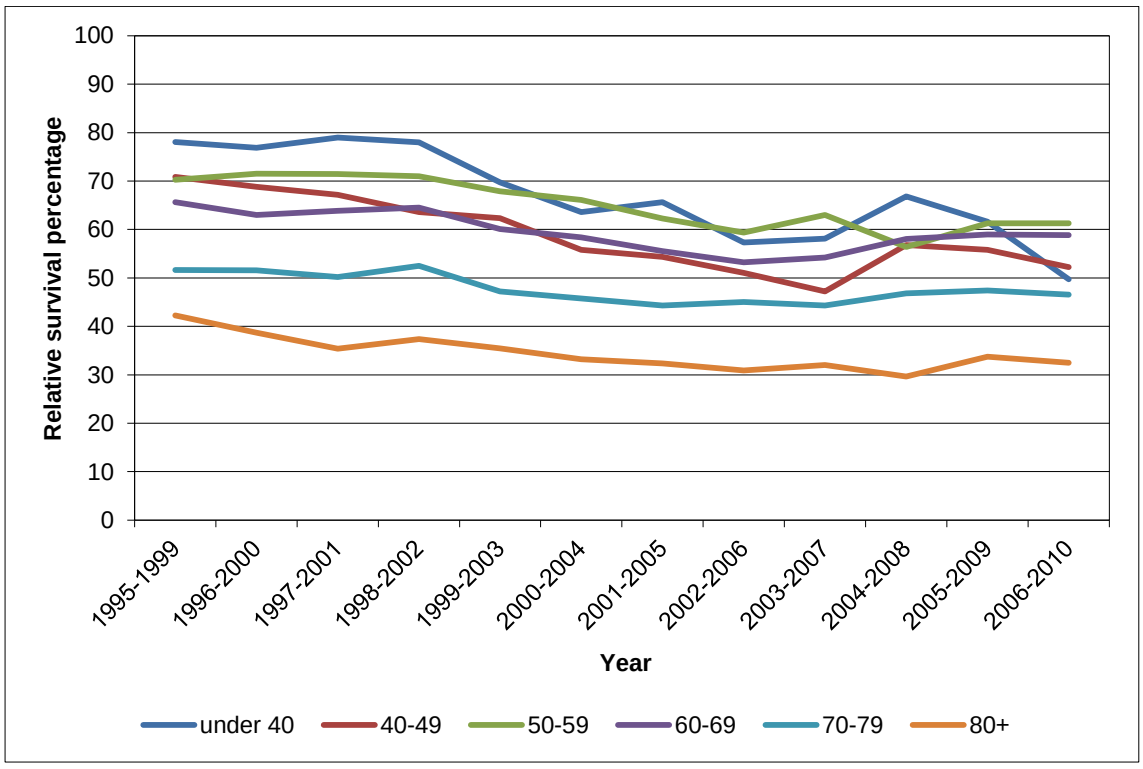
Figure 25: Five-year relative survival from bladder cancer (ICD-10 code C67) by age, in men, England 1995-2010.



Source: NCRS

Figure 26: Five-year relative survival from bladder cancer (ICD-10 code C67) by age, in women, England 1995-2010.



Source: NCRS

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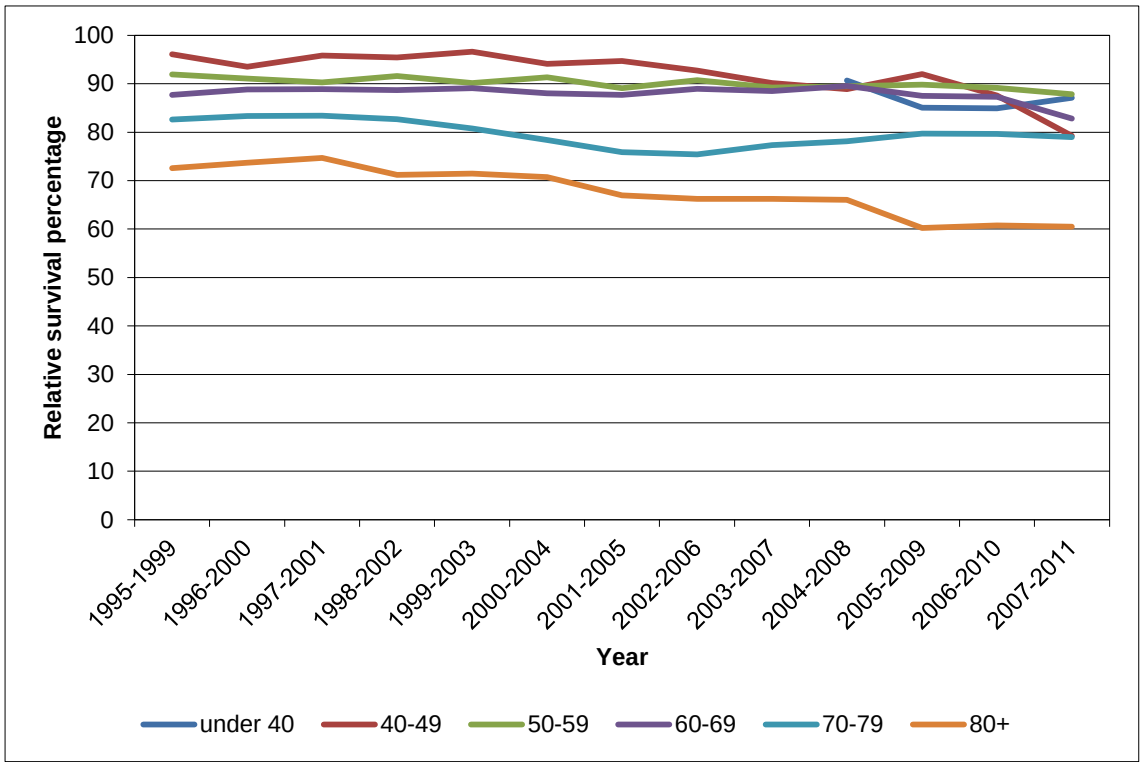
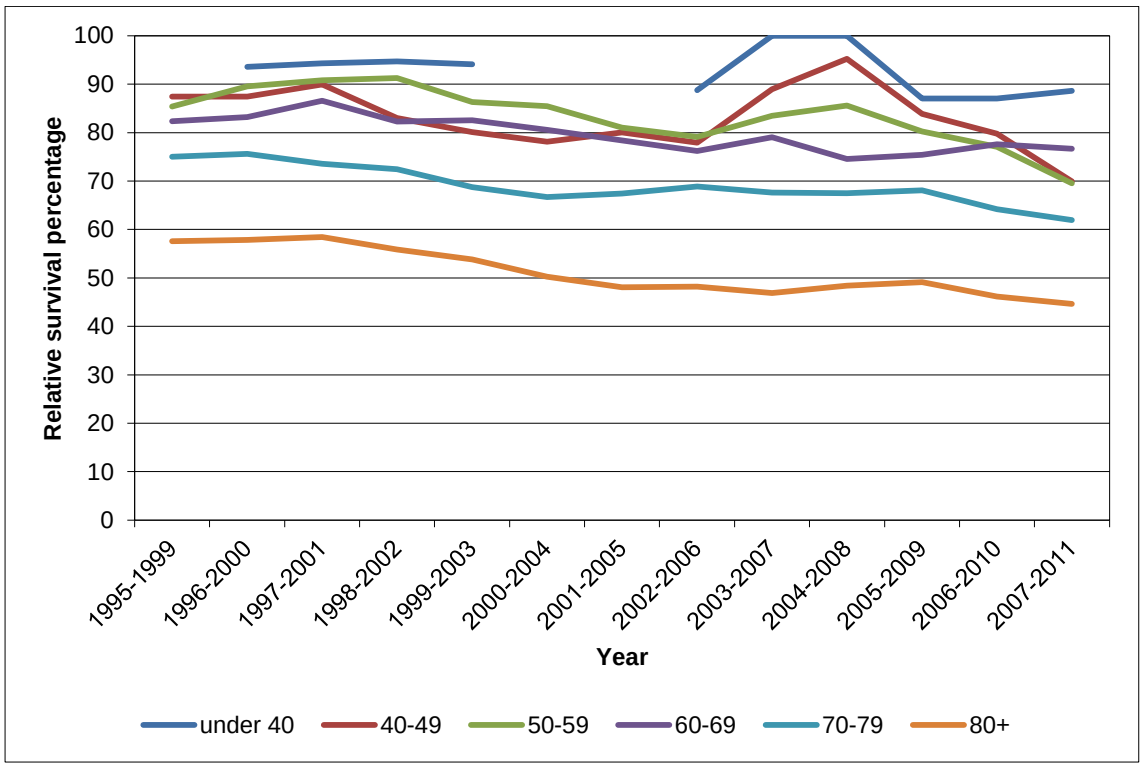
Figure 27: One-year relative survival from bladder cancer (ICD-10 code C67) by age, in men, Wales 1995-2011.



Source: WCISU

Figure 28: One-year relative survival from bladder cancer (ICD-10 code C67) by age, in women, Wales 1995-2011.



Source: WCISU

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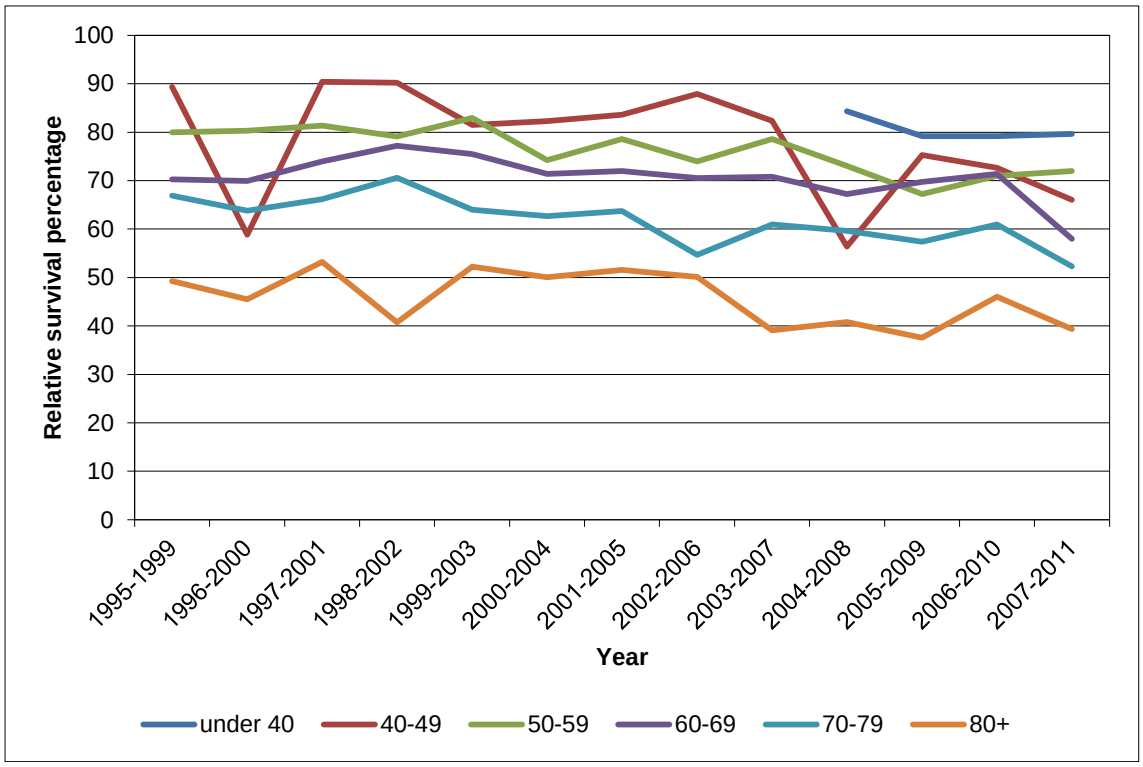
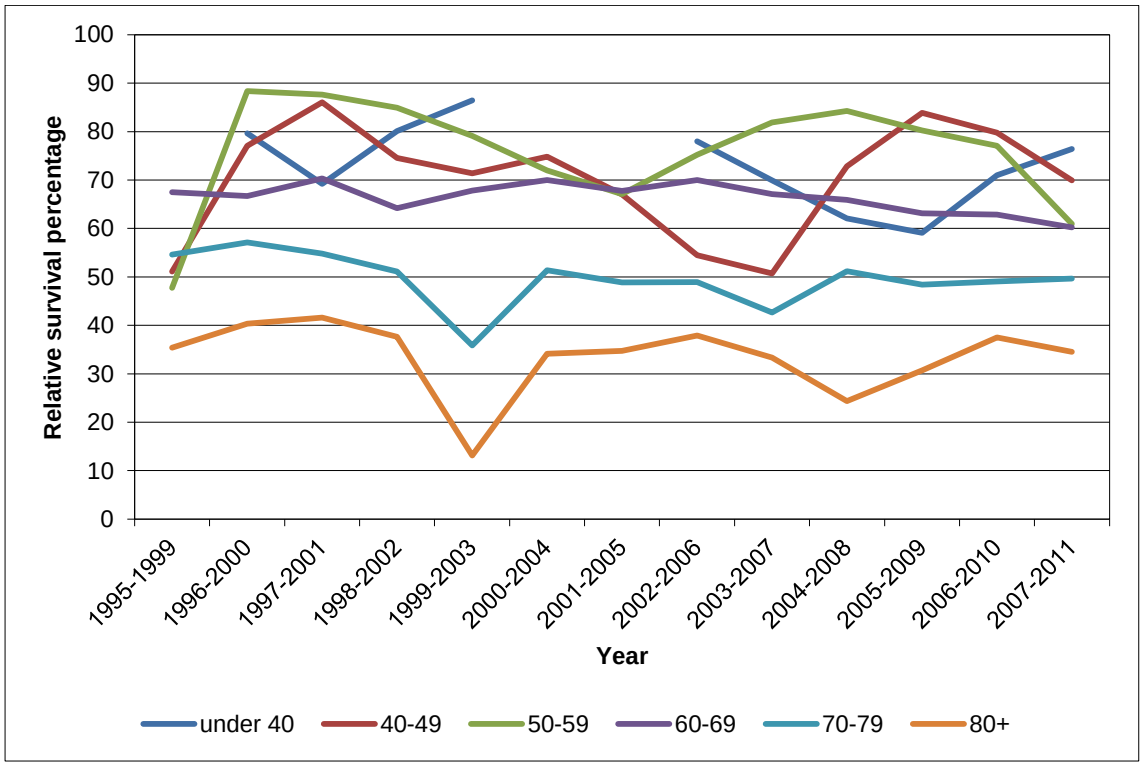
Figure 29: Five-year relative survival from bladder cancer (ICD-10 code C67) by age, in men, Wales 1995-2011.



Source: WCISU

Figure 30: Five-year relative survival from bladder cancer (ICD-10 code C67) by age, in women, Wales 1995-2011.



Source: WCISU

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In England there is a consistent pattern of decreasing relative survival with increasing quintile of income deprivation. In men, one-year survival in 2006-10 was 78% in the least deprived quintile and 75% in the most deprived. In women, one-year survival in 2006-10 was 69% in the least deprived and 59% in the most deprived. Confidence intervals on these rates do not overlap, indicating that the differences are due to more than chance variation.

In men, five-year survival in 2006-10 was 60% in the least deprived quintile and 55% in the most deprived. However the confidence intervals overlap so we cannot be sure that this difference is not just chance variation. In women, five-year survival in 2006-10 was 51% in the least deprived and 42% in the most deprived. Here confidence intervals do not overlap, indicating that the differences are due to a true underlying difference.

In Wales in 2007-11 there is not a pattern of survival by deprivation; in contrast to England. The highest one-year survival for men was 79% in quintile 2, compared to 73% in the most deprived quintile. However, confidence intervals overlap on all quintiles. Survival for women was highest in quintile 2 at 72%, and lowest in quintile 4 at 52%. The confidence intervals do not overlap so this is likely to be a true difference.

Patterns are similar for five-year survival in Wales. Men in quintile 2 have the highest survival at 61% and men in quintile 4 the lowest at 42%, but confidence intervals overlap. Women in quintile 2 have the highest survival at 62% and women in quintile 4 the lowest at 36%. As with one-year survival the confidence intervals do not overlap so this is likely to be a true difference.

Survival decreases with increasing stage at diagnosis. This may help explain the poorer survival in women, as they are more likely to be diagnosed at an advanced stage. As described in the incidence section nearly 1 in 3 bladder cancer diagnoses in England and 1 in 10 in Wales are made at stage IV, which has poor outcomes.

In England in 2006-10 the relative survival at one year for stage IV disease was 42% in men and 34% in women, whilst five-year survival was 11% in men and 12% in women (Figures 31 and 32).

In Wales in 2007-11 one-year survival for stage IV disease was 56% for men and 54% for women. Five-year survival was 28% for men and 36% for women (Figures 33 and 34). The confidence intervals in these calculations are large, indicating a higher degree of uncertainty, and it is not possible to be sure that there is a survival difference between England and Wales.

Non muscle-invasive disease (stage I) shows better outcomes then muscle-invasive disease (stage II-IV), with one-year survival of 95% in men and 91% in women in England (Figure 31). Five-year survival was 79% and 76% (Figure 32). The difference between NMIBC and MIBC is particularly apparent at five years of follow-up where the survival for stage II bladder cancer is nearly half that of stage I (Figure 32). In Wales one-year survival for stage I disease was 91% in men and 89% in women; five-year survival was 66% and 76% respectively (Figures 33 and 34).

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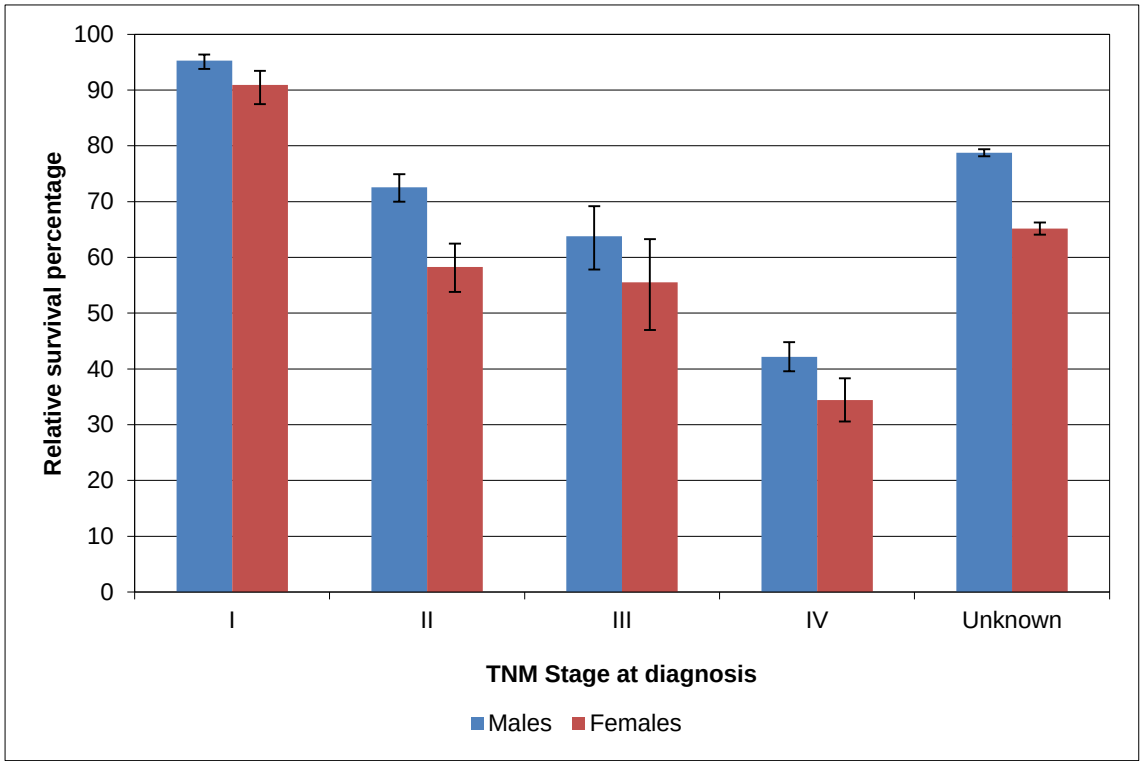
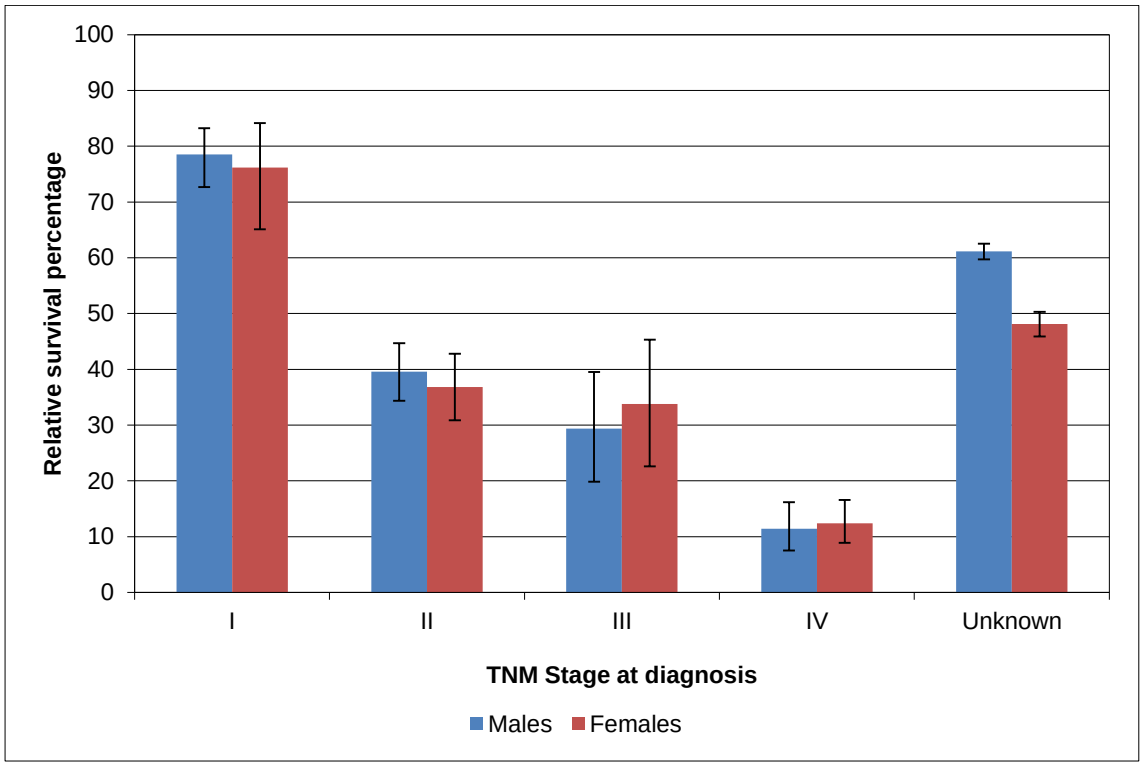
Figure 31: One-year relative survival from bladder cancer (ICD-10 code C67) by stage at diagnosis, England 2006-2010.



Source: NCRS

Figure 32: Five-year relative survival from bladder cancer (ICD-10 code C67) by stage at diagnosis, England 2006-2010.



Source: NCRS

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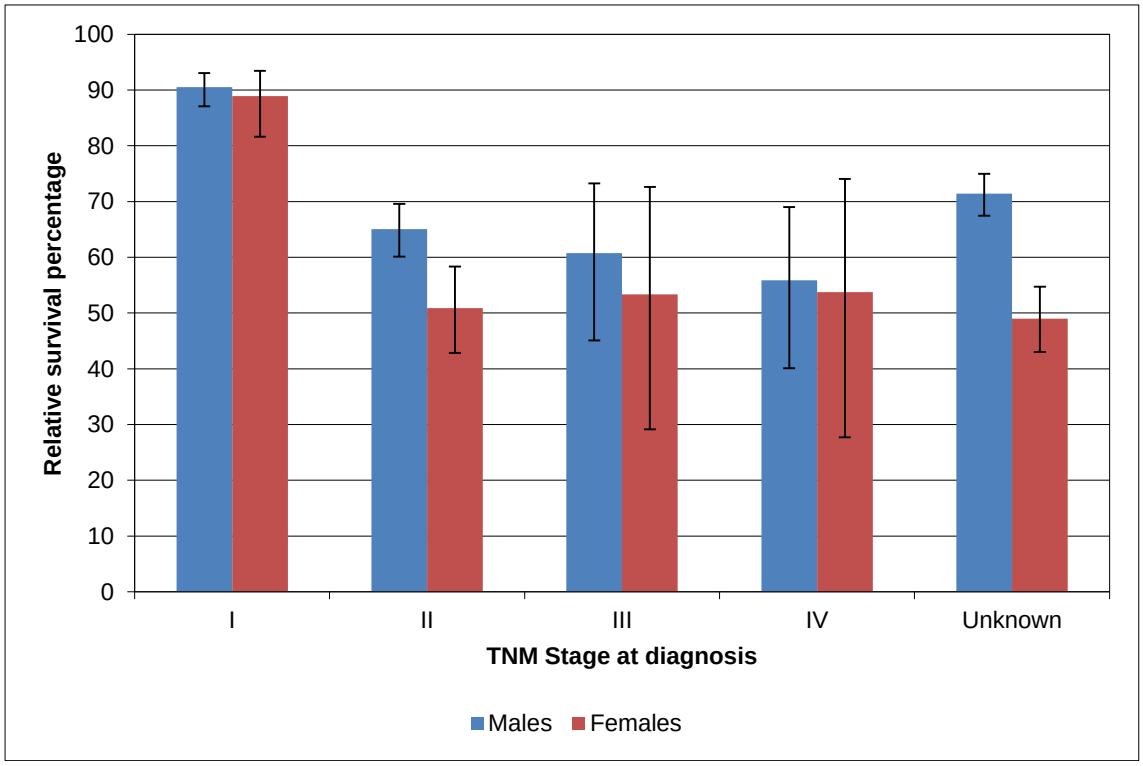
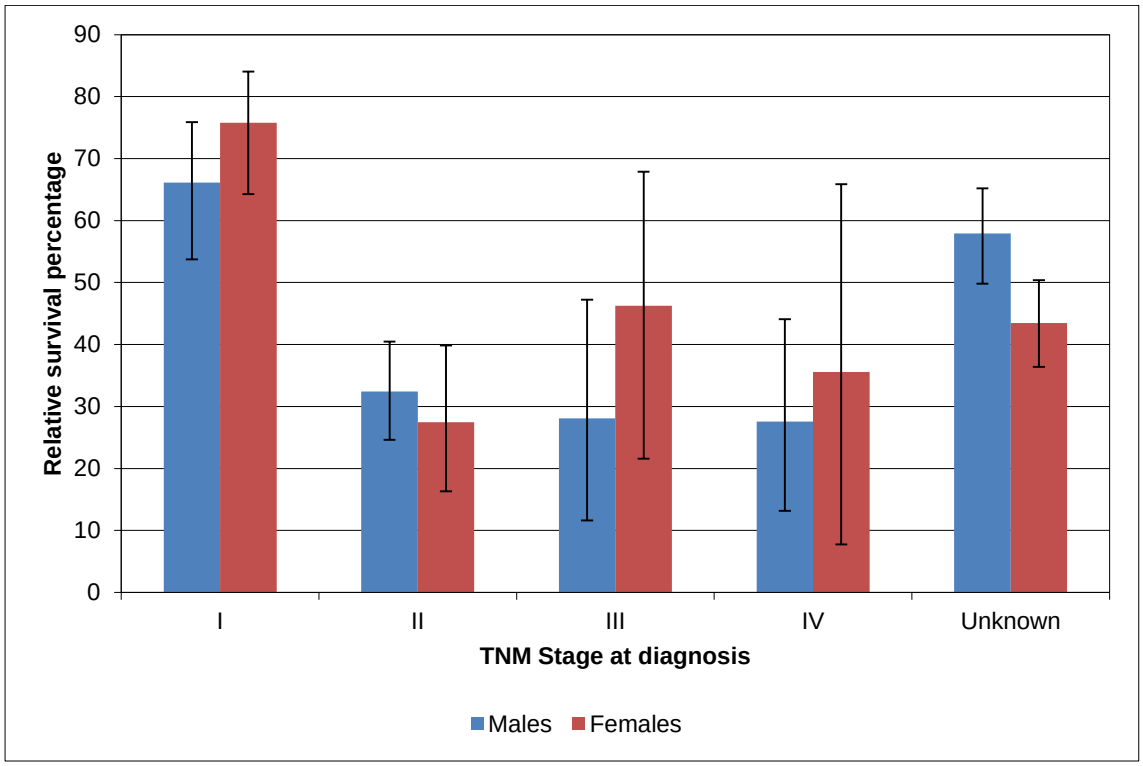
Figure 33: One-year relative survival from bladder cancer (ICD-10 code C67) by stage at diagnosis, Wales 2007-2011.



Source: WCISU

Figure 34: Five-year relative survival from bladder cancer (ICD-10 code C67) by stage at diagnosis, Wales 2007-2011.



Source: WCISU

One-year relative survival in men at CCG level varies from 60% to 96%, with the range for women 28% to 87%. There is greater uncertainty with survival calculations so fewer CCGs

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are statistically significantly different from the England average than with incidence or mortality data.

Five-year relative survival in men at CCG level varies from 21% to 87%, with the range for women 0% to 76%.

There is no obvious geographical pattern in terms of CCGs which have higher or lower survival, although some CCGs with poorer one-year survival also have poorer five-year survival; as might be expected.

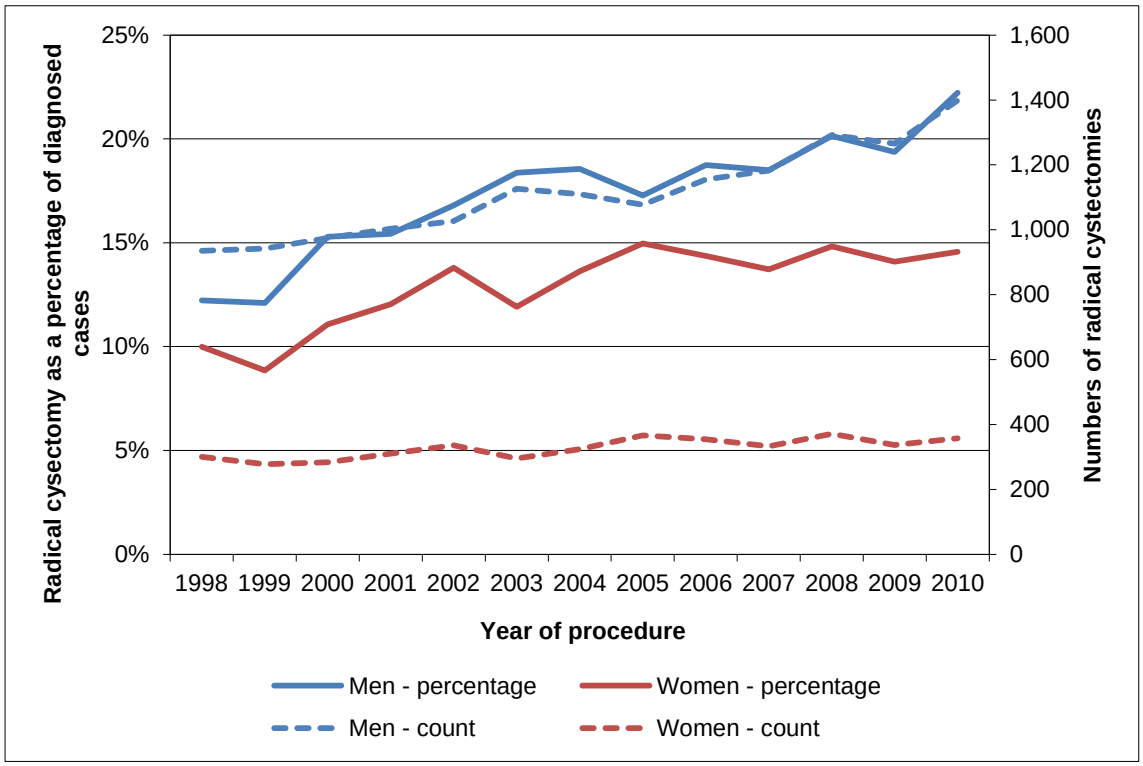
1.6 Treatment

Treatment data were only available for England.

Radical cystectomy is the complete removal of the bladder. It is one of the main treatments for muscle-invasive bladder cancer.

Numbers of radical cystectomies have risen in men from 935 in 1998 to 1,399 in 2012. In women the rise in number has been smaller; 300 operations were done in 1998 compared to 357 in 2012. As a proportion of cases diagnosed in that year the rate of radical cystectomy in men was 15% in 2000 compared to 22% in 2010 ($p<0.001$), with the proportion in women 11% and 15% respectively ($p<0.001$). Regression analysis indicates a linear increase in cystectomy rate of 4.2% each year for men and 3.5% for women ($p<0.05$ for both) (Figure 35).

Figure 35: Radical cystectomy for bladder cancer (ICD-10 code C67), England 1998-2010.



Source: HES; NCRS

The proportion of people aged under 70 who have cystectomy is similar; given the smaller numbers there is inherent instability in the rates for younger ages. The cystectomy rate is lowest in those aged 80 and over at diagnosis: 3% of men and 2% of women.

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In men all age groups have shown a linear increase in cystectomy rate ($p<0.05$). The annual increase in rates ranged from 4.4%-8.7% but with fairly wide confidence intervals, so it is not possible to say that one age range increased more or less than another.

In women the cystectomy rate in those aged under 40 and 80+ did not change over the time period; although numbers in the youngest age group are very small. In women aged 60-69 analysis indicated that the data was best described by an increasing rate to 2002 followed by no change until 2010. The cystectomy rate in women aged 50-59 and 70-79 showed a linear increase of 3.2% and 5.6% respectively ($p<0.05$).

Cystectomy rates are higher in the least deprived men, compared to the most deprived ($p<0.001$). The proportion of men in the least deprived quintile who had cystectomy was 26% compared to 20%. However, women were equally likely to receive a cystectomy whichever deprivation group they were in.

The cystectomy rate increased linearly in each deprivation quintile for both men and women ($p<0.05$). This varied between 5.8%-7.3% in men and 4.4%-6.7% in women. There is no evidence that the rate increased more quickly or slowly with variation in deprivation.

Radiotherapy is also a frequently used treatment modality for muscle-invasive bladder cancer. Radiotherapy is also used for symptomatic relief of advanced bladder cancer, so it is important to differentiate between curative and palliative intent.

Data shown here is based on the number of radiotherapy treatment courses delivered in 2009 and 2010 as a proportion of diagnoses in those same years. This means that those diagnosed prior to 2009 are not represented, nor any treatment after 2010. This restriction is required as the radiotherapy data holds little demographic detail such as age and sex, so must be linked to diagnosis data.

The proportion of men having curative radiotherapy is higher than in women, but the difference is fairly small; 11.3% in men compared to 9.5% in women ($p<0.001$). The proportion having palliative radiotherapy is close to being statistically significant ($p=0.06$) but again the magnitude of any difference is small; 11.2% in men and 12.2% in women (Figure 36).

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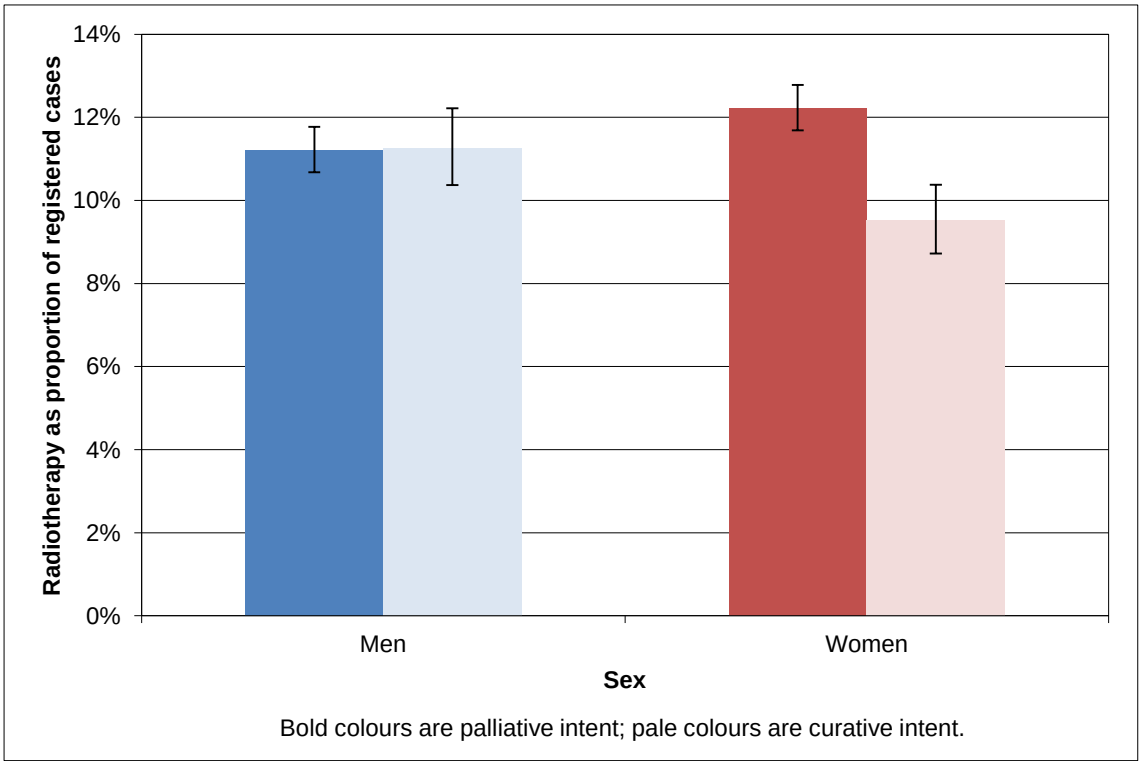
Figure 36: Radiotherapy for bladder cancer (ICD-10 code C67) by sex, England 2009-2010.



Source: RTDS; NCDR

Data for radiotherapy by age are more difficult to interpret as numbers are smaller. In both sexes palliative radiotherapy is high in those aged 80+ with a corresponding dip in curative radiotherapy. In the three older age-bands, which include the majority of cases, the usage of palliative radiotherapy increases with age (Figure 37).

There is no strong evidence of any trend in radiotherapy use by quintile of deprivation.

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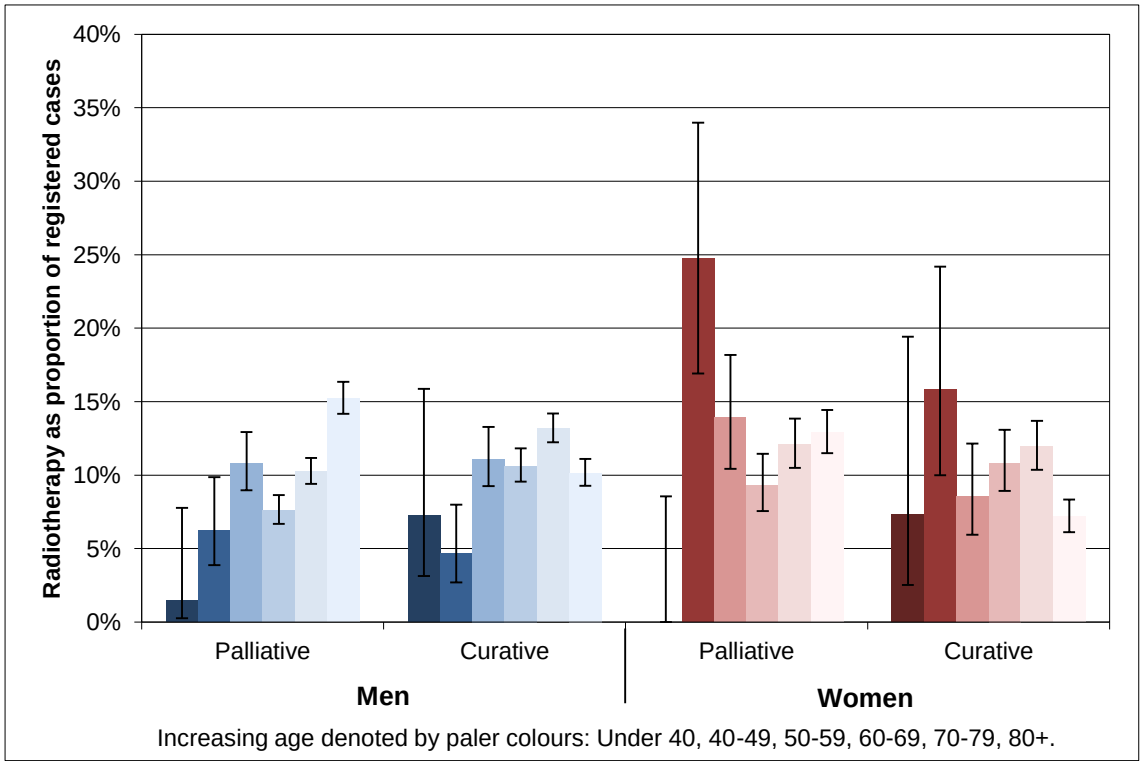
Figure 37: Radiotherapy for bladder cancer (ICD-10 code C67) by age and sex, England 2009-2010.



Source: RTDS; NCDR

Chemotherapy may be used for bladder cancer before surgery or radiotherapy (neo-adjuvant) or afterwards (adjuvant). It may also be used for palliative care, but unlike the radiotherapy data this is not recorded in the dataset. Chemotherapy data here comes from outpatient HES data which is only available from 2003 onwards.

The proportion of patients who receive chemotherapy has risen since 2003. In 2003 2% of men and 1% of women had any chemotherapy recorded, but in 2010 this was 9% and 7% respectively. Figure 38 suggests that the increase has been faster since 2007, but small numbers and limited time period mean that there is no statistical evidence to confirm this. The Cochrane systematic review supporting the use of neo-adjuvant chemotherapy in bladder cancer was published in 2007. It is also important to bear in mind that recording of chemotherapy in HES may have variable completeness over time, and better evidence will be available with the upcoming Systemic Anti-Cancer Therapy (SACT) dataset.

Analysis by age and deprivation group does not indicate a statistically significant difference in recorded chemotherapy use by these factors. Regression models indicate that all groups have shown an increase in recorded chemotherapy with time ($p<0.05$ for all). This increase has been between 24% and 45% in men by age group; 20% and 48% in women by age group; 30% and 34% in men by deprivation quintile; and, between 20% and 42% in women by deprivation quintile.

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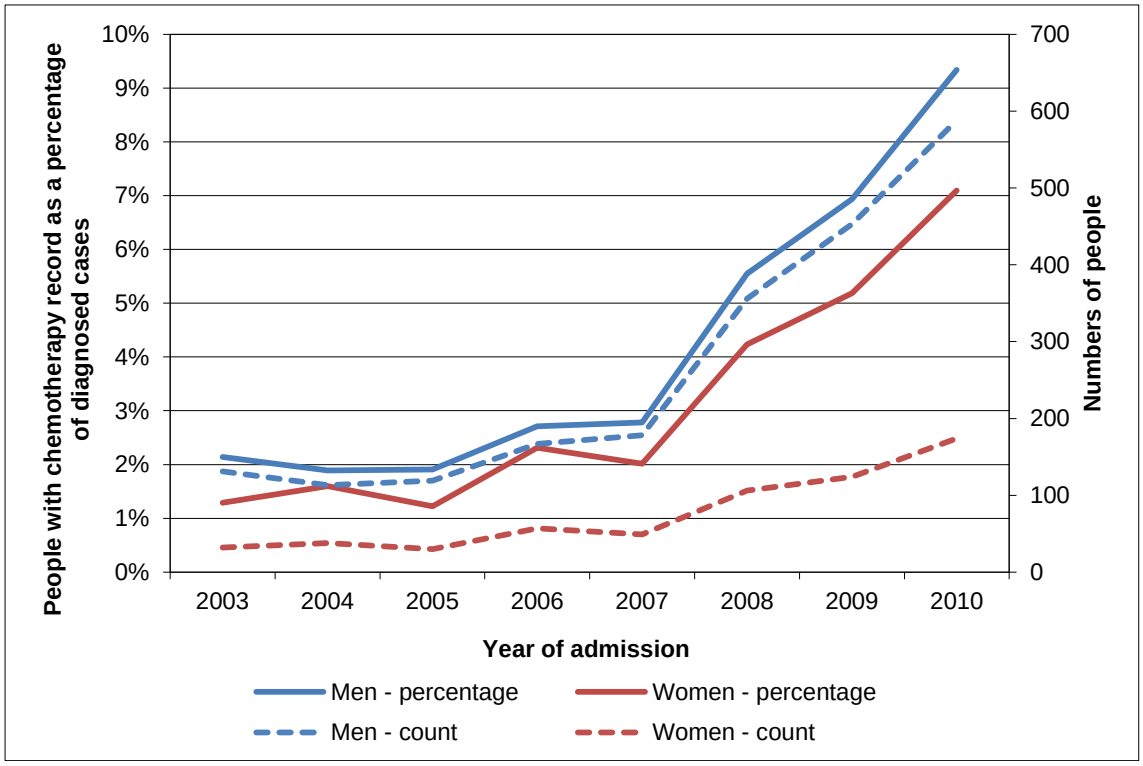
Figure 38: Chemotherapy for bladder cancer (ICD-10 code C67) by sex, England 2003-2010.



Source: HES; NCDR

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2 Patient centred care

The principle of 'patient-centred care' has for a long time been embedded and enshrined in the 7 Key Principles of the NHS Constitution as well as in other key NHS policies and practice guidance. This approach has been reflected in the strengthening commitment to providing holistic needs assessments. In March 2011, the national cancer action team published a guide for healthcare professional on holistic needs assessment for people with cancer in which Professor Mike Richards wrote:

"Holistic needs assessment should be part of every cancer patient's care. It can make a huge difference to a patient's overall experience and has the potential to improve outcomes by identifying and resolving issues quickly"".

A growing body of evidence from other cancers supports the patient-centred approach as enhancing outcomes with respect to patients' psychological, emotional and social wellbeing. Further research also suggests that better information and support, alongside greater involvement in decision making and exercising choice in their treatment, can also have a positive, and measurably beneficial, effect on clinical outcomes. In addition, evidence and research points to the highly significant contribution of the clinical nurse specialist, or a key worker, in providing information and support to people with cancer and their resultant level of patient satisfaction.

NICE has established a set of quality standards on Patient experience in adult NHS service (NICE 2012), which aims to raise the quality of the overall patient experience. However there remain significant variations in performance and standards between trusts.

Throughout this guideline, we have emphasised the importance of discussion between the person who has bladder cancer and those involved in their care and the principle of shared decision making and informed patient choice.

Wherever we have done so, there is also an assumption, even where not specifically stated, that if the person with bladder cancer so wishes, they should be able to be accompanied in such discussions by their partner/carer or another supporter. This will be particularly important at points throughout the treatment pathway when potentially distressing information is being shared; for example at first diagnosis of cancer or when difficult decisions are being made. Examples of difficult decisions include choices relating to treatments such as intravesical BCG, radical cystectomy, radical radiotherapy or chemotherapy or choices about palliative care or entry into clinical trials. Some treatments may have implications for survival or life changing impacts on sexual health, relationships and body image and the patient may therefore want to discuss these with those closest to them.

There is an assumption, even where not specifically stated, that all patients should be offered the opportunity to participate in clinical trials and research, wherever possible.

2.1 Patient satisfaction

The National Patient Experience Surveys have shown that compared to people with prostate cancer the experience of people with other urological cancers, of whom the majority have bladder cancer seems to be worse.

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

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Clinical evidence (see also full evidence review)

Study quality and results

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

Evidence statements

Data from the National Cancer Patient Experience Survey (NCPES) 2011/12 National Report was used to answer this review question. Compared to other cancer patients, urological cancer patients (including those with bladder and kidney cancer but excluding prostate cancer) were least likely to report being offered a written assessment and care plan or to be provided with information about self-help or support groups. Urological cancer patients were also least likely to be given the contact details of their CNS (Table 6). There were pronounced differences in views between those patients with a CNS and those without one in terms of verbal and written information, involvement, information on financial support and prescriptions, discharge information, post discharge care, and emotional support. This indicates that the presence of a CNS makes a positive difference to the perceived quality of cancer services and may be a reason for the comparatively low levels of patient satisfaction for urological cancer patients. In an analysis of 41,441 responses to one question from the 2010 NCPES, one study (El Turabi et al., 2013) reported that bladder cancer patients were among the least likely to report a positive experience of involvement in treatment decision making (Table 7).

Table 6: Areas in the NCPES where urological cancer patients gave less positive assessments (less than average scores) as compared to other cancer groups

NCPES question	Average (range) % across all cancer groups	Urological cancers %
When you were first told that you had cancer, had you been told you could bring a family member or friend with you?	72% (61% to 80%)	65%
Given written information about the type of cancer that they had which was easy to understand?	69% (50% to 78%)	66%
Given a choice of different types of treatment?	84% (75% to 90%)	75%
Do you think your views were taken into account when the team of doctors and nurses caring for you were discussing which treatment you should have?	70% (64% to 76%)	65%
Were the possible side effects of treatment(s) explained in a way you could understand?	75% (69% to 79%)	69%
Were you given written information about the side effects of treatment(s)?	81% (67% to 90%)	70%
Were you given the name of a Clinical Nurse Specialist who would be in charge of your care?	87% (75% to 93%)	75%
Did hospital staff give you information about support or self-help groups for people with cancer?	82% (65% to 89%)	65%
Did hospital staff give you information about how to get financial help or any benefits you might be entitled to?	52% (29% to 70%)	29%
Did hospital staff tell you that you could get free prescriptions?	73% (50% to 82%)	61%
After leaving hospital, were you given enough care and help from health or social services (For example, district	61% (51% to 68%)	51%

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NCPES question	Average (range) % across all cancer groups	Urological cancers %
nurses, home helps or physiotherapists?		
Have you been offered a written assessment and care plan?	24% (20% to 27%)	20%

Table 7: Variation of patient experience of involvement in treatment decision making within urological cancers (El Turabi et al., 2013)

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

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

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer clinical nurse specialist support to people with bladder cancer and give them the clinical nurse specialist's contact details.** **Ensure that the clinical nurse specialist:** • **acts as the key worker to address the person's information and care needs** • **has experience and training in bladder cancer care.** **Trusts should consider conducting annual bladder cancer patient satisfaction surveys developed by their urology multidisciplinary team and people with bladder cancer, and use the results to guide a programme of quality improvement.** **Clinicians caring for people with bladder cancer should ensure that there is close liaison between secondary and primary care with respect to ongoing and community-based support.**
Relative value placed on the outcomes considered	Patient satisfaction was the focus of this review question. It is a very important consideration because of the comparatively low levels of bladder cancer patient satisfaction reported in the National Cancer Patient Experience Survey (NCPES). The GDG also considered the role of Clinical Nurse Specialists (CNS) in patient satisfaction and the potential impact of providing information and support on CNS workload.
Quality of the evidence	The NCPES was used for this review question, which was considered to be of moderate to high quality as it is a national survey completed by over 70,000 patients. The main limitation of the survey is that responses from bladder cancer patients are included in the broader category of urological cancers, so it

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	was not possible to identify satisfaction scores specifically from bladder cancer patients. Moderate quality evidence from one study which analysed data from the 2010 NCPES reported that within urological cancers patient involvement in decision-making was lowest for bladder cancer patients. The NCPES indicated that for all cancers, CNS input was associated with greater patient satisfaction, and there are low levels of patient satisfaction and access to a CNS within urological cancers. Therefore, it was recommended that access to a CNS is provided for all bladder cancer patients. The recommendation that the CNS should have experience and training in bladder cancer was based on the GDG's clinical experience. It was considered important to specify this due to the broad remit of urology nurse specialists working in several disease sites and sub-specialties. The GDG made a research recommendation because there was a lack of evidence to answer the review question. The research recommendation that bladder cancer patient results be separated out from other urological cancers in nationally collected datasets aims to facilitate understanding of the issues related to patient satisfaction for bladder cancer. The research recommendation should also provide data about the causative and contributory factors that result in the comparatively low levels of patient satisfaction for bladder cancer patients. The lack of evidence about bladder cancer specifically lead to the research recommendation being made. No health economic evidence was identified.
Trade-off between clinical benefits and harms	The GDG considered the benefits of the recommendations to be greater patient satisfaction, better shared decision-making, and improved information and support, which could lead to improved clinical patient outcomes. No harms were identified by the GDG. The National Patient Experience Surveys have shown that compared to people with prostate cancer the experience of people with other urological cancers, of whom the majority have bladder cancer, seems to be worse. This led the GDG to try to identify the causative and contributory factors for this. The GDG noted that the main limitation of the National Cancer Patient Experience Survey is that responses from bladder cancer patients are included in the broader category of urological cancers, so it is not possible to identify satisfaction scores specifically from bladder cancer patients. Consequently the GDG were unable to identify the causative/contributory factors for the low satisfaction levels reported by bladder cancer patients. However the GDG felt it was important that this question was answered. They agreed that recommending annual satisfaction surveys of bladder cancer patients would be the first step in obtaining data, specific to people with bladder cancer that could give insight into the causative/contributory factors for the reported low levels of satisfaction.

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Trade-off between net health benefits and resource use	No health economic model was developed for this topic. However, the GDG acknowledged that there are potential costs associated with the recommendations made. Most notably from the increase in CNS capacity and training costs required to implement the recommendations. The provision of information for patients may also incur some costs, as will the implementation of local patient satisfaction surveys and subsequent quality improvement programmes. The GDG balanced these costs against the potential savings from fewer patient complaints. The recommendations may also have a potential positive impact on patient outcomes and reduced time on avoidable enquiries for both patients and clinical staff.
Other considerations	The recommendations were developed to address any inequalities and ensure universal CNS access to all bladder cancer patients. Data from the NCPES demonstrates that around 25% of urological cancer patients were not given name of a CNS and a high proportion of patients were not given advice about financial benefits etc. Therefore, the GDG considered that significant change in practice in terms of CNS support to bladder cancer patients will be required. Also, CNS training specifically for bladder cancer will need to be expanded. The GDG were made aware of CNS census data that suggests that urological nurse specialists see an average of 176 newly diagnosed urological cancer patients a year, compared to around 94 patients per year in gynaecological cancer. The recommendations attempt to address this imbalance across cancer sites. The GDG were also aware that communication between primary and secondary care is often unsatisfactory, in particular, updates on significant events in secondary care (for example change of disease stage or treatment) may not reach primary care in a timely fashion. This can result in primary care teams not being able to provide proper support to distressed people. In view of this, the GDG felt strongly that the need for close liason between the two sectors had to be stressed.

Research recommendation	**What are the causative and contributory factors underlying the persistently very low levels of reported patient satisfaction for bladder cancer?**
Why is this important	The urological cancers grouping (which includes bladder cancer but excludes prostate cancer) has consistently appeared near the bottom of the table of patient satisfaction comparisons of all cancer types in national patient experience surveys. Prostate cancer (which is also managed in urological services) is recorded separately and has continued to appear near the top of the tables. It is uncertain why this is the case, except that there is now an accepted link between the level of clinical nurse specialist allocation, information and support provision and patient satisfaction. The urological cancers grouping has the lowest level of clinical nurse specialist allocation in comparison with all other cancer types or groupings (including prostate cancer). The prolonged pattern of intrusive procedures that dominate investigation, treatment and follow-up regimens for bladder cancer may also contribute to this position. Additionally, there is concern that people with bladder cancer at or near the end of life, who are by that stage often quite frail and elderly, may not always have access to the full range of

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Research recommendation	What are the causative and contributory factors underlying the persistently very low levels of reported patient satisfaction for bladder cancer?
	palliative and urological support and may, at times, be treated in general wards in hospital and experience significant symptoms of pain and bleeding (haematuria). To explore this research question bladder cancer patients need to be identified separately from the generic group of urological cancer patients in nationally collected data sets.

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

People with bladder cancer have a wide spectrum of information and support needs, dependant on the stage of their cancer and their treatments and follow-up options. These treatment and follow-up options may have marked physical, psychological, sexual and social implications for the patient, which emphasises the need for specialist information and support.

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

Clinical evidence (see also full evidence review)

Study quality and results

Low quality evidence from six studies were included: three studies were qualitative interview studies, two studies used questionnaires to collect data, and one study reported data from a randomised trial. Details of the included studies are summarised in Table 8.

Evidence statement

In four studies (Fitch *et al.,* 2010; Mansson *et al.,* 1991; Kressin *et al.,* 2010; Ronaldson, 2004), data were collected from 76 bladder cancer patients who had undergone radical cystectomy. Common physical and psychological post-operative issues reported by patients included the ability to self-manage urinary diversion, adjustment to body image, and changes in sexual function. In one UK study (Dearing, 2005) of 78 patients with superficial bladder cancer (pTa or pT1), 47% were aware of their underlying diagnosis. 33% of the 55 smoking patients had been told to stop smoking by their general practitioner and 7% had been told to stop by their urologist. Faithful *et al.* (2001) reported patient satisfaction and quality of life from a randomised trial of nurse-led or conventional follow-up in 115 men treated with radical radiotherapy for prostate or bladder cancer. The nurse-led protocol focused on coping with symptoms and provided continuity of care and telephone support. There were few differences between groups in terms of overall quality of life. However, men in the nurse-led group were significantly more satisfied with their follow-up care than men in the control group. The nurse-led clinic was perceived as providing a greater amount of information. Patients liked the continuity of care provided and the fact that their families could be included in the consultation.

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Table 8: Summary of included studies

Study	Population	Methods	Analysis	Relevance to guideline population	Key findings
Fitch et al. (2010)	Well reported	Well reported	Well reported and rigorous analysis	Canadian cohort. Patients interviewed after cystectomy and urinary diversion to explore experiences and perceptions of living with changes following surgery.	Adjustments to body image, sexual function, management of incontinence or leakage were important issues for patients. Patients wanted more information about what to expect after urinary diversion and how to self-manage post-operative problems. Highlighted the need for opportunity to discuss body image and sexuality changes in open communication with health professionals.
Mansson et al. (1991)	Well reported	Poorly reported – limited information about interview procedure	Poorly reported – no details of analysis and no supporting quotes from participants	Swedish cohort. Patients interviewed after cystectomy to explore post-operative adjustment, psychological and emotional changes.	Majority of patients reported difficulty in post-operative period, with physical or psychological problems, and difficulty with stoma/collection bag. Sexual function had changed in many patients which some reported to have had a negative impact on their relationship. 14 patients reported negative change in mood. Self-esteem diminished in 7 patients.
Kressin et al. (2010)	Poorly reported (abstract only)	Poorly reported (abstract only)	Poorly reported (abstract only)	USA cohort. Women who had undergone cystectomy completed Sexual Function questionnaire	Conference poster abstract only. 7/14 (50%) were not sexually active, commonly due to low libido. Sexual function score corresponded to poor function. 85% received no sexual counselling prior to surgery. 71% (10/14) would have wanted to be counselled.
Dearing (2005)	Poorly reported – no details of respondents	Adequately reported	Adequately reported	UK cohort. Patients with non-muscle invasive bladder cancer having follow-up cystoscopy.	51% of patients were unaware of their diagnosis, having been informed they had ‘warts’ or ‘bleeding areas’ in the bladder. Of the ‘ever’ smokers, 12 (22%) were aware that smoking was a risk factor for the development of bladder cancer, and 7 (13%) were aware that continued smoking could worsen prognosis. 18 (33%) had been told to stop smoking, for any reason by their GP and 4 (7%) had been told to stop by urologist.

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Study	Population	Methods	Analysis	Relevance to guideline population	Key findings
Ronaldson (2004)	Poorly reported – no details of respondents	Adequately reported	Adequately reported	UK cohort. Patients who had undergone cystectomy and ileal conduit diversion in the last 6 years	Mostly positive feedback regarding in-patient stays and pre-operative information. Stoma care nurse was highly praised. Several concerns were expressed related to difficulty with confidence, mood changes, living with urostomy and initial impact on their lives. Fear of leaking bags, dressing differently, restricted activities, depression and other concerns about follow-up and the fear of further cancer.
Faithful et al. (2001)	Well reported	Well reported	Well reported and rigorous analysis	UK cohort. Majority population were men undergoing radiotherapy for prostate cancer.	Symptom scores were similar between patients receiving nurse-led or conventional follow-up. Those who received nurse-led follow-up were significantly more satisfied and valued the continuity of care.

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Follow the recommendations on communication and patient-centred care in NICE's guideline on patient experience in adult NHS services and the advice in NICE's guidelines on improving outcomes in urological cancers and improving supportive and palliative care for adults with cancer throughout the person's care.** **Use a holistic needs assessment to identify an individualised package of information and support for people with bladder cancer and, if they wish, their partners, families or carers, at key points in their care such as:** • **when they are first diagnosed** • **after they have had their first treatment** • **if their bladder cancer recurs or progresses** • **if their treatment is changed** • **if palliative or end of life care is being discussed.** **When carrying out a holistic needs assessment, recognise that many of the symptoms, investigations and treatments for bladder cancer affect the urogenital organs and may be distressing and intrusive. Discuss with the person:** • **the type, stage and grade of their cancer and likely prognosis** • **treatment and follow-up options** • **the potential complications of intrusive procedures, including urinary retention, urinary infection, pain, bleeding or need for a catheter** • **the impact of treatment on their sexual health and body image, including how to find support and information relevant to their gender** • **diet and lifestyle, including physical activity** • **smoking cessation for people who smoke (see section 2.4)** • **how to find information about bladder cancer, for example through information prescriptions, sources of written information, websites or DVDs** • **how to find support groups and survivorship programmes** • **how to find information about returning to work after treatment for cancer** • **how to find information about financial support (such as free prescriptions and industrial compensation schemes).** **Offer people with bladder cancer and, if they wish, their partners, families or carers, opportunities to have discussions at any stage during their treatment and care with:** • **a range of specialist healthcare professionals, including those who can provide psychological support** • **other people with bladder cancer who have had similar**

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	treatments. **Offer people with bladder cancer and, if they wish, their partners, families or carers, opportunities to have discussions with a stoma care nurse before and after radical cystectomy as needed.**
Relative value placed on the outcomes considered	The GDG considered the most important issue to be patient and/or carer satisfaction (with communication, information support and treatment received). The following issues were also considered to be important: • Health-related quality of life (inc. patient and carer-reported outcomes) • Understanding/knowledge of disease and treatment • Psychological factors (e.g. distress, coping) • Perceived social support • Informed choice and decision-making • Ability to self-manage condition/side-effects • Referral to support groups/networks These issues were identified in the literature review and were strongly voiced by the patient/carer representatives on the GDG. Referral to support groups and social support were specified as issues in the PICO but were not reported in the evidence. Social support, financial advice (compensation scheme), talking to other patients, and holistic needs assessment were issues that were not reported in the evidence but the GDG used their clinical knowledge, patient experience and knowledge of other sources of information on patient experience (such as patient experience surveys) to make recommendations on these issues.
Quality of the evidence	All evidence was assessed as being of low quality using the NICE methodology checklist for qualitative studies. The main limitation of the evidence was that there was no direct evidence to answer review question. Most studies included patients having cystectomy so there was a lack of evidence from patients with non-muscle invasive disease. The included qualitative studies were also limited by small sample sizes. The GDG is aware of other studies in which patient information and support needs were met by health professionals other than the CNS, but this was not the focus of this review question. The GDG drew upon their clinical knowledge and patient experience to form recommendations in the absence of any direct high quality evidence. The GDG made the recommendations about providing opportunities to talk to other patients, referral to support groups and holistic needs assessment based on their clinical experience. Also the recommendation to provide financial advice including industrial compensation was based on GDG experience because one of the best described risk factors for bladder cancer is occupational exposure to chemicals used in industry. Patients exposed in this way may be eligible for compensation through the Industrial Injuries Disablement Benefits Scheme.

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	The GDG specifically highlighted this as many patients and their clinicians may not be familiar with this entitlement. Moreover, recognition of occupational risk is important epidemiologically to assess the effectiveness of health and safety legislation. No health economic evidence was identified.
Trade-off between clinical benefits and harms	The GDG considered the main clinical benefits of the recommendations to be: improved patient satisfaction, psychological and social well-being; empowerment of patients to participate in the management of their disease; improved equality of care; reduced sense of loss of independence; and enhanced patient-felt locus of control. The GDG also considered that there is a potential for increased patient anxiety from receiving too much information. The GDG considered it important to achieve a balance between the types of advice given and the strength of the evidence base which underpins them. The GDG felt that currently many patients do not get holistic needs assessment and opportunities for reviewing patients' needs during the patient pathway are missed. Emphasising the patient perspective was thought to outweighs the potential harms. The GDG agreed that it is important to improve patient satisfaction and considered that few people are likely to have information overload
Trade-off between net health benefits and resource use	No health economic evidence was identified for this topic and no economic model was developed. The GDG considered that the potential costs of the recommendations include: increased resource to provide patient information and support; increased time to do holistic needs assessment; increased costs from providing resources such as booklets; and an increase in free prescriptions The potential savings include: fewer patient complaints; reduced time on avoidable enquiries; less inappropriate treatment and investigation The GDG considered that the benefits in terms of patient well-being justify the potential additional costs. It is unknown whether there will be a net cost or saving.
Other considerations	The GDG recommended individualised holistic needs assessment with the expectation that health professionals will take into account patient specific needs such as for translation, health literacy, and help with a full range of disabilities. The GDG noted that there needs to be gender relevant sexual advice because there is a concern that advice about sexual function has been focused on men. The GDG felt that holistic needs assessment would address many potential areas of inequality. The GDG expect that a considerable increase in the use of holistic needs assessment and associated resources will result from these recommendations. There will be an increased need for uro-oncology CNS time and other specialists. The GDG also considered the existing NICE guidance, notably the Improving Outcomes Guidance for Urological Cancers and the Cancer Service Guideline for Supportive and Palliative Care.

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2.3 Specialist palliative care needs at end of life

People with bladder cancer approaching the end of life may experience particular physical symptoms, such as intractable bleeding, obstruction and pain, and associated psychological distress. This can create specific end of life care needs for bladder cancer patients, in addition to their more general physical, psychological and spiritual palliative care needs.

The management of specific symptoms related to locally advanced bladder cancer are discussed in Chapter 6.

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

Clinical evidence (see also full evidence review)

Study quality and results

Six studies were identified, including one systematic review and five cross-sectional questionnaire studies. Details of the included studies are summarised in table 9.

Evidence statements

In three studies, the respondents were carers of cancer patients who had received palliative care. The study by Fakhoury *et al.* (1997) reports carer's (n=1858) satisfaction with community nurses, hospital doctors and GPs, but does not specify that patients were treated within a specialist palliative care team. Most carers were highly satisfied with the different providers, but the least satisfaction was reported by those who cared for patients with genito-urinary tumours. Duration of pain was not related to any of the satisfaction measures. In a study of 181 patients, Teunissen *et al.* (2006) reported that the main support needs in palliative care for all ages was the need for functional support and support in coping. Older patients (aged 70 or over) reported less need for relational support or support in communication than younger respondents. A Swedish study of 379 women who had lost their husband/partner to prostate or bladder cancer reported that 93% of patients had adequate access to pain control during the last 3 months of life, whereas only 33% had access to psychological support. The cancer patient's mental health status at the end-of-life was also predictive of the widows' anxiety and depression at follow-up (Valdimarsdottir *et al.*, 2002).

A Japanese study including 469 bereaved family members of cancer patients rated that 25% of patients experienced a mild self-perceived burden, and 25% experienced moderate to severe self-perceived burden. Family members rated care strategies to alleviate patient-perceived burden, the most useful being 1) eliminating pain and other symptoms that restrict patient activity; 2) quickly disposing of urine and stools so that they are out of sight; 3) supporting patients' efforts to care for themselves (Akazawa *et al.*, 2010). One systematic review aimed to explore self-care strategies in end-of-life care in advanced cancer (Johnston *et al.*, 2009). Although self- care strategies such as using information and using distraction techniques were identified these were largely initiated by researchers. No research used a patient-centred approach and the author concluded that self-care in advanced cancer is an under-explored area. Factors that prevented patients to self-care were low education, poor socio-economic status, psychological distress and physical limitations.

One study of a UK urology ward's inpatients and outpatients (n=881) with advanced or metastatic urological cancer reported that 75% of out-patients had specific problems or were generally unwell as a result of their disease and would have benefitted from specialist palliative care. 25% were well at the time of their visit but potential psychosocial problems arising from coping with terminal disease were not addressed (Brierly & O'Brien, 2008).

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Table 9: Summary of included studies

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

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**A member of the treating team should offer people with incurable bladder cancer a sensitive explanation that their disease cannot be cured and refer them to the urology multidisciplinary team.** **Tell the primary care team that the person has been given a diagnosis of incurable bladder cancer within 24 hours of telling the person.** **A member of the urology multidisciplinary team should discuss the prognosis and management options with people with incurable bladder cancer.** **Discuss palliative care services with people with incurable bladder cancer and if needed and they agree, refer them to a specialist palliative care team (for more information see recommendations in section 2.2 on holistic needs assessment and NICE's guidelines on improving supportive and palliative care for adults with cancer and improving outcomes in urological cancers).** **Offer people with symptomatic incurable bladder cancer access to a urological team with the full range of options for managing symptoms.**
Relative value placed on the outcomes considered	The GDG considered all aspects of the modified PICO table as important. The GDG considered it crucial that patient and carer information and support needs are met during end-of-life care. It was also felt important that the person's primary care team were informed of the diagnosis to enable them to support the person and their family. The GDG emphasised the importance of psychological well-being and quality of life as well as relief from symptoms such as bleeding and pain. The evidence presented for this review question was very limited and there was no evidence specific to bladder cancer. There was no evidence about informed choice/decision-making or about referral to support groups/networks.
Quality of the evidence	The quality of the evidence was assessed as being of low quality using the NICE methodology checklist for qualitative studies. The limitations of the evidence were mainly related to the lack of good data to answer the review question. None of the studies were specific to bladder cancer. Only one study was about urological cancer. The included studies were qualitative interview studies or cross-sectional questionnaire studies, a majority of which were conducted in a non-UK setting and did not specify if care was provided by a specialist palliative care team. The published systematic review that was presented concluded that there is a lack of evidence about self-care in advanced cancer. The lack of direct evidence meant that the GDG had to base their

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	recommendations upon clinical consensus. The GDG noted that access to the specialist palliative care team was central to the recommendations, with a view to ensuring that there is rapid access and effective liaison between teams. This is also in line with existing NICE guidance (Improving Outcomes in Urological Cancer and Supportive and Palliative care). The GDG considered the specific issues for bladder cancer patients such as bleeding, haematuria and bladder irrigation which require urological input while under the care of the palliative team One study presented in the evidence review also suggested that there may be lack of psychosocial support for urological cancer patients with advanced disease. No research recommendation was made.
Trade-off between clinical benefits and harms	The potential benefits of the recommendations include greater informed patient choice, better symptom control, improved access to information and psychosocial and spiritual support during palliative care. Efficient referral to the appropriate team (e.g. urological input) may also reduce inappropriate treatment. The GDG also considered that if the patient has improved end-of-life care there is a potential benefit to bereaved relatives in terms of reduced distress. The GDG considered a potential harm from engaging the patient and their family in conversations about their prognosis and palliative care is that this could be very distressing. The GDG noted that recent information suggests not all patients wish to be informed of their diagnosis of incurable disease. The GDG balanced the benefits against the harms by considering that it is vital that patients are offered a full and sensitive explanation about their prognosis and options for palliative treatment. The GDG considered that, for the majority, the benefits of improved support during palliative care and referral to the appropriate clinicians outweigh any potential harms, but that patient consent should be acquired before making a palliative care referral.
Trade-off between net health benefits and resource use	No health economic model was developed for this topic and no economic evidence was identified. The GDG considered the potential costs of the recommendations to be from increased palliative care activity (e.g. more referrals) and clinical nurse specialist involvement. There may also be increased NHS community care costs. The potential savings are likely to arise from reduced hospital-based costs, reduced bed days and admissions. The GDG considered there may be fewer investigations and a potential reduction in futile treatments The GDG considered that there is likely to be net saving to the NHS.
Other considerations	The GDG considered equalities issues about access to palliative care services from minority ethnic groups and according to age. The recommendations made should help address any inequalities by enabling access to palliative care for all patients with incurable bladder cancer. The GDG also considered the existing NICE guidance, notably the Improving Outcomes Guidance for Urological Cancers, the Cancer Service Guideline for Supportive and Palliative Care. The GDG considered that it is likely to require considerable change in

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	practice to implement the recommendations. The GDG highlighted the shortage of CNSs for urological cancers as a potential issue in the implementation of the guideline. There is likely to be an increase in input from palliative care teams and uro-oncology CNSs for patients with incurable disease.

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

Compared to non-smokers, smokers have approximately three times the risk of developing bladder cancer. People who stop smoking reduce their risk of developing bladder cancer by 30-60% within four years. Given the relationship between smoking and bladder cancer, there is an opportunity to discuss a person's smoking history during consultations about bladder cancer.

For people with bladder cancer who smoke, other potential benefits of smoking cessation include reduction in the risk of developing other smoking-related cancers and cardiorespiratory disease, improved efficacy of radical radiotherapy and reduction in peri-operative risk for radical cystectomy.

The timing of discussions about smoking and smoking cessation may be difficult to judge in view of the distress and anxiety caused by a new diagnosis of bladder cancer and associated treatment decisions.

Given the association between smoking and bladder cancer, and the known benefits of smoking cessation, experts have questioned whether smoking cessation would reduce the risk of progression and recurrence in people with bladder cancer.

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

Clinical evidence (see also full evidence review)

Study quality and results

One systematic review (Crivelli *et al.*, 2014) and a further three prognostic studies (Kim *et al.*, 2014; Wyszynski *et al.*, 2014; Wang *et al.*, 2014) were identified for the outcomes of recurrence, progression, cancer-specific survival, overall survival and treatment-related morbidity. One study presenting baseline data from a randomised trial (Ditre *et al.,* 2011) was identified for the outcome of health-related quality of life. The systematic review was clearly focused and relevant to the review question for this topic. However, many of the included studies focused on the impact of patients' smoking status on clinical outcomes rather than the effect of smoking cessation. The literature search was judged to be sufficiently rigorous and the methodology was well reported. No formal study quality assessment was reported in the systematic review. However, the studies were limited by heterogeneity in patient characteristics (i.e. stage and grade), follow-up time, and the categorization of smoking status, which precluded a meta-analysis. The use of intravesical therapy and repeat TURBT also varied across studies and was often not reported. The study by Ditre *et al.* (2011) was considered to be of low quality because the population was not relevant to the review question (the majority of participants had lung or breast cancer). Study quality for the three further prognostic studies was assessed using the NICE methodology checklist for prognostic studies. The quality assessment item regarding loss to follow-up was not considered relevant to this review question. In all studies the study sample was clearly defined and represented the population of interest. All studies used an appropriate method of analysis and hazard ratios (HRs) were provided. A narrative summary of the evidence is presented.

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Evidence statements

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

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

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

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

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

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer smoking cessation support to all people with bladder cancer who smoke, in line with NICE's guidelines on smoking cessation services and brief interventions and referral for smoking cessation.**
Relative value placed on the outcomes considered	The GDG considered recurrence, progression, and survival to be the most important outcomes. Recurrence was considered to be important because it necessitates more cystoscopies, follow-up, and treatment. Therefore, reductions in recurrence can be very beneficial to patients

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	and the NHS. Likewise, progression is important because it is associated with worse outcomes for patients and further treatment. Overall survival was considered to be important as it is a crucial aspect for most medical interventions. There were no outcomes from the PICO that were not reported in the evidence and no additional outcomes (i.e. not specified in the PICO) were used to make recommendations. Quality of life and treatment-related morbidity were not considered to be useful once the evidence was appraised. This was because there was limited evidence in this area.
Quality of the evidence	The systematic review was assessed as being of high quality using the NICE methodology checklist for systematic reviews, although no formal study quality assessment of individual studies was reported in the review. The quality of the additional prognostic studies was assessed as being of high quality using the NICE methodology checklist for prognostic studies. The study reporting quality of life data was considered to be low quality because the population was not relevant to the review question (the majority of participants had lung or breast cancer). Although the evidence was generally assessed as being of good quality using the NICE checklists, the reviewer highlighted some potential issues with the evidence. Most notably, many of the studies included in the systematic review focused on the impact of patients' smoking status on clinical outcomes rather than the effect of smoking cessation. Also, different definitions of smoking cessation were used in the studies and patient populations were heterogeneous, which prevented the pooling of data. In addition, there were a very small number of events for progression, which may reduce the power to observe an effect. The data on overall survival was limited because only eight studies reported this outcome, and only two of these studies showed an impact of smoking on overall survival. A further limitation was that the follow-up periods in the studies were highly variable. A general lack of long-term follow-up also reduces the power of events observed. The GDG noted these limitations and they affected the recommendations that were made. The GDG felt they could only make general recommendations (PH1). The different definitions of smoking cessation proved particularly troublesome. The GDG felt this prevented them from drawing stronger conclusions because the data on patients who quit smoking could not be pooled. The GDG made a research recommendation because they wanted to address the limited availability of data on the impact of smoking cessation, particularly on progression and overall survival. Furthermore, the GDG considered that getting a definitive answer on whether offering smoking cessation interventions improves bladder cancer specific outcomes was very important. Despite the limitations of the evidence base (significant enough to warrant a research recommendation), the GDG wanted to make a recommendation in this area. The GDG felt this was appropriate as the recommendation is in line with existing NICE guidance and there is a low likelihood of harmful effects associated with recommending smoking cessation.
Trade-off between clinical benefits and	The GDG considered the potential benefits of the recommendation to be accrued by current smokers that decide to give up smoking. The primary

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harms	potential benefits were identified as a reduction in recurrence and progression and an improvement in overall survival. The GDG also felt that there may be further benefits associated with reduced complication rates after surgery. The GDG considered the potential harms of the recommendation to be an increase in patient anxiety and weight gain after smoking cessation. In balancing the potential harms and benefits, the GDG felt that the potential benefits strongly outweighed the potential harms. This is because improved survival and potentially a reduced need for further treatment is likely to be far more important to patients and the NHS than a potential for weight gain and anxiety.
Trade-off between net health benefits and resource use	A health economic evaluation was not conducted for this topic and no suitable health economic data was identified in the literature review. However when making their decision, the GDG did consider the potential costs and savings of the recommendations. The GDG recognised that there would be some costs associated with the smoking cessation interventions but felt that they were relatively cheap. In addition, the recommendation is line with existing guidance and so smoking cessation support should already be offered. The GDG considered one of the economic benefits to be a reduced need for medical interventions, including general anaesthetic, cystoscopy, intravesical therapy, imaging, cystectomy and radiotherapy. The GDG felt that a further benefit could be a reduction in post-operative complications. Overall, the GDG felt that there was unlikely to be any substantial increase in costs as a result of the recommendation. This is because smoking cessation interventions are relatively cheap and are likely to be offset by a reduced need for medical interventions and a reduction in post-operative complications.
Other considerations	In terms of equalities concerns, the GDG noted that the prevalence of smoking is higher in more deprived groups who are also less likely to give up smoking following the offer of interventions. The GDG further noted that bladder cancer incidence increases and relative survival decreases with increasing deprivation The GDG also thought that there could be a potential language barrier to people whose first language is not English. The GDG also considered the possibility of any changes in practice necessitated to implement recommendations. The GDG believes that smoking cessation is not routinely offered in urology clinics to all bladder cancer patients who smoke. Therefore, there may be a need for further resources in these clinics to support smoking cessation. However, all patients should be advised to quit smoking according to current NICE guidance. Communication between primary and secondary/tertiary care needs to be strengthened to support smoking cessation in bladder cancer patients. When making their recommendations, the GDG also considered the well-evidenced general health and economic benefits from smoking cessation.

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Research recommendation	In people with newly diagnosed bladder cancer who smoke, is an enhanced smoking cessation programme more effective than a standard programme in terms of bladder cancer recurrence, progression and overall survival
Why is this important	The benefits of smoking cessation are well described, in terms of general health. The causative link between smoking and bladder cancer is also well known. There is also evidence that stopping smoking after the diagnosis of bladder cancer reduces risk of recurrence. this may be the case for those with bladder cancer. A diagnosis of bladder cancer for people who smoke therefore allows them the opportunity to help themselves by taking the opportunity to stop smoking, and reduce their risk of recurrence. This research will examine whether an enhanced cessation programme is more effective than the current standard cessation support.

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3 Diagnosing and staging bladder cancer

3.1 Endoscopic Assessment

Bladder cancer is usually identified during a telescopic check of the bladder (cystoscopy), under local anaesthetic. The light source routinely used during the procedure produces white light. Bladder cancer is occasionally missed during cystoscopy. Therefore other technologies have been proposed to try to improve the accuracy of cystoscopy.

Two new technologies to enhance the accuracy of cystoscopy are photodynamic diagnosis and narrow band imaging. Both technologies aim to make visual assessment of the bladder more accurate.

Photodynamic diagnosis requires the instillation of a photosensitiser compound into the bladder shortly before cystoscopy. This compound is absorbed more strongly by bladder cancer than by the normal bladder lining and fluoresces bright pink when a special blue light is used at cystoscopy. This makes it easier to see bladder cancer.

Narrow band imaging uses a processor to filter out all but the blue and green light wavelengths. This has the effect of sharpening the contrast between normal tissue and bladder cancer. It does not require any prior preparation such as a photosensitiser.

Neither of these technologies is currently widely used in the NHS.

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

Clinical evidence (see also full evidence review)

Study quality and results

A Health Technology Assessment (HTA) was identified (Mowatt *et al.*, 2010), which reviewed the diagnostic accuracy of photodynamic diagnosis (PDD) and white light cystoscopy (WLC). 27 studies (from 36 reports) were included in the HTA review and a further four studies were identified from the literature search. The reference standard for studies of diagnostic accuracy was histopathological examination of biopsied tissue. A summary of the pooled estimate results from the HTA are shown in Tables 10 and 11. A systematic review of the diagnostic accuracy of narrow band imaging (NBI) and WLC was identified (Zheng *et al.*, 2012) and the results are provided in Tables 12, 13, and 14. Evidence for recurrence was gathered from one systematic review of raw data of WLC and Hexaminolevulinate (HAL) PDD (Burger *et al.*, 2013) and one randomised trial of NBI and WLC (Naselli *et al.*, 2012). Recurrence data are provided in tables 15 and 16.

Evidence statements

Photodynamic diagnosis (PDD) versus white light cystoscopy (WLC)

Diagnostic accuracy

In both patient and biopsy based detection of bladder cancer PDD had a higher sensitivity but lower specificity than WLC (Mowatt et al., 2010). Five studies (370 patients) reported patient-based detection. In the pooled estimates the sensitivity for PDD was 92% (95% CI 80% to 100%) compared with 71% (95% CI 49% to 93%) for WLC, whereas the specificity for PDD was 57% (95% CI 36% to 79%) compared with 72% (95% CI 47% to 96%) for WLC, with the CIs for the two techniques overlapping. A total of 14 studies (1746 patients) reported biopsy-based detection (number of biopsies: 8574 for PDD analysis, 8473 for WLC

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analysis). In the pooled estimates the sensitivity for PDD was 93% (95% CI 90% to 96%) compared with 65% (95% CI 55% to 74%) for WLC, whereas the specificity for PDD was 60% (95% CI 49% to 71%) compared with 81% (95% CI 73% to 90%) for WLC. The pair of CIs for both sensitivity and specificity did not overlap, providing evidence of a difference in diagnostic performance between the techniques. The point estimates of the patient-level analysis were similar to those from the biopsy-level analysis, although the intervals were substantially wider, as might be expected because of the smaller number of studies and observations available for this level of analysis (moderate quality evidence).

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

Side effects of photosensitising agent used

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

Recurrence

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

Narrow band imaging (NBI) versus white light cystoscopy (WLC)

Diagnostic accuracy

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

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

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

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

Recurrence

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

Process-related morbidity/health-related quality of life

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

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

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

Abbreviations: CI, confidence interval; DOR, diagnostic odds ratio.

Table 11: Summary of pooled estimate results for PDD and WLC for biopsy-based detection of bladder cancer (reported in Mowatt et al., 2010)

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

Table 12: Summary of pooled estimate results for NBI and WLC for patient-based detection of bladder cancer (reported in Zheng et al. 2012)

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

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; DOR, diagnostic odds ratio.

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Table 13: Summary of pooled estimate results for NBI and WLC for biopsy-based detection of bladder cancer (reported in Zheng et al 2012)

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

Table 14: Summary of pooled estimate results for NBI for patient-based detection of CIS (reported in Zheng et al. 2012)

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

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Table 15: GRADE evidence profile: What are the most effective endoscopic techniques for diagnosing bladder cancer. Comparison: hexaminolevulinate (HAL) photodynamic diagnosis (PDD) versus white light cystoscopy (WLC)

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

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

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Table 16: GRADE evidence profile: What are the most effective endoscopic techniques for diagnosis bladder cancer. Comparison: narrow band imaging (NBI) versus white light cystoscopy (WLC)

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

[1] Naselli et al. 2012 [2] Small sample size / Low number of events

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Cost-effectiveness evidence

The primary results of the analysis by Mowatt et al. 2010 are summarised in the table 17. While the study is of methodologically high quality, there were concerns about the use of life years as the primary effectiveness measure in the majority of analyses. This makes cost-effectiveness difficult to assess as there is no established cost-effectiveness threshold based on life years in the UK.

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

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

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

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

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

Overall, it is difficult to fully and robustly assess cost-effectiveness in this area. However, it does appear that strategies involving urinary biomarkers, cytology or PDD provide additional benefits compared to current practice and do so at a cost that society might be willing to pay. Of particular note to the topic at hand is that photodynamic diagnosis (PDD) appears to be a cost-effective alternative to WLC as an initial diagnostic test.

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Table 17: Modified GRADE table showing the included evidence (Mowatt et al. 2010) comparing urine tests and endoscopic techniques in the diagnosis of new and recurrent bladder cancer

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

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Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		12. CSC_CTL_PDD (CTL_WLC)	£1,859	11.65 LYs	£401	0	Dominated	Throughout the analyses, one of the following strategies was the most cost-effective strategy (assuming a threshold of £30,000 per life year): CTL_WLC (CTL_WLC) CTL_PDD (CTL_PDD) IMM_PDD (IMM_WLC) FISH_PDD (FISH_WLC) CSC_FISH_PDD (FISH_WLC) CSC_PDD (CSC_WLC) CSC_IMM_PDD (IMM_WLC) Probabilistic sensitivity analyses In addition, a probabilistic sensitivity analysis (PSA) was conducted for both the base case analysis and the sensitivity analysis where QALYs are		
		13. CSC_WLC (CSC_WLC)	£1,920	11.60 LYs	£462	-0.04	Dominated			
		14. CSC_IMM_WLC (IMM_WLC)	£1,941	11.63 LYs	£483	-0.02	Dominated			
		15. CSC_CTL_WLC (CSC_WLC)	£1,997	11.62 LYs	£539	-0.03	Dominated			
		16. CSC_FISH_PDD (FISH_WLC)	£2,005	11.66 LYs	£547	0.01	£60,284			
		17. CSC_FISH_WLC (CSC_WLC)	£2,042	11.63 LYs	£37	-0.03	Dominated			
		18. CSC_NMP22_WLC (CSC_WLC)	£2,070	11.62 LYs	£65	-0.03	Dominated			
		19. CSC_PDD (CSC_WLC)	£2,082	11.63 LYs	£77	-0.03	Dominated			
		20. CSC_NMP22_PDD (NMP22_WLC)	£2,089	11.65 LYs	£84	-0.01	Dominated			
		21. CSC_IMM_WLC (CSC_WLC)	£2,105	11.63 LYs	£100	-0.03	Dominated			
		22.CSC_CTL_PDD (CSC_WLC)	£2,145	11.64 LYs	£140	-0.01	Dominated			
		23. CSC_IMM_PDD (IMM_WLC)	£2,195	11.66 LYs	£190	<0.01	£309,256			

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Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		24. CSC_FISH_PDD (CSC_WLC)	£2,270	11.66 LYs	£75	0	Dominated	used. In both analyses, the PSA results demonstrated considerable uncertainty. Indeed, there was no clear strategy that would be preferred based on the PSA results. However, in the analysis using QALYs, three strategies were found to have around a 20% probability of being cost-effective over much of the thresholds; CTL-WLC (CTL-WLC), FISH-PDD (FISH-WLC) and CSC-FISH-WLC (FISH-WLC).		
		25. CSC_NMP22_PDD (CSC_WLC)	£2,318	11.65 LYs	£123	-0.01	Dominated			
		26. CSC_IMM_PDD (CSC_WLC)	£2,370	11.65 LYs	£175	<0.01	£237,863			
		Base case analysis results without dominated and extendedly dominated options (using LYs as effectiveness measure)								
		1. CTL_WLC (CTL_WLC)	£1,043	11.59 LYs	-					
		2. CTL_PDD (CTL_WLC)	£1,094	11.60 LYs	£51	0.01	£3,423			
		4. FISH_PDD (FISH_WLC)	£1,235	11.64 LYs	£141	0.04	£3,806			
		8. IMM_PDD (IMM_WLC)	£1,458	11.65 LYs	£223	0.01	£28,864			
		16. CSC_FISH_PDD (FISH_WLC)	£2,005	11.66 LYs	£547	0.01	£60,284			
		26. CSC_IMM_PDD (CSC_WLC)	£2,370	11.65 LYs	£365	<0.01	£270,375			
		Sensitivity analysis using quality adjusted life years [QALYs] as effectiveness measure								
		1. CTL_WLC (CTL_WLC)	£1,043	9.00 QALYs	-					
		2. CTL_PDD (CTL_WLC)	£1,094	9.01 QALYs	£51	0.01	£4,678			
		4. FISH_PDD	£1,235	9.04	£141	0.03	£5,051			

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Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		(FISH_WLC)		QALYs						
		8. IMM_PDD (IMM_WLC)	£1,458	9.04 QALYs	£223	<0.01	Extendedly dominated			
		16. CSC_FISH_PDD (FISH_WLC)	£2,005	9.05 QALYs	£770	0.01	£66,905			
		19. CSC_PDD (CSC_WLC)	£2,082	9.01 QALYs	£77	-0.04	Dominated			
		23. CSC_IMM_PDD (IMM_WLC)	£2,195	9.05 QALYs	£190	0	Dominated			
		26. CSC_IMM_PDD (CSC_WLC)	£2,370	9.05 QALYs	£365	0	Dominated			
	Comments: The majority of the analyses use life years as the measure of the effectiveness. Quality adjusted life years (QALYs) are the preferred effectiveness measure of NICE.									

Abbreviations and notation:

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

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

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

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

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Recommendations	**Offer white-light-guided TURBT with one of photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker test (such as UroVysion using fluorescence in-situ hybridization [FISH], ImmunoCyt or a nuclear matrix protein 22 [NMP22] test) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT.**
Relative value placed on the outcomes considered	All outcomes specified in the PICO were reported in the evidence. Sensitivity, specificity, and recurrence were considered by the GDG to be the most important outcomes. Sensitivity and specificity provide information about the accuracy of the test in detecting bladder cancer. Recurrence is a measure of the efficacy of the test. Morbidity was not considered to be an important outcome because all patients have to undergo cystoscopy. Consideration was given to the need for a catheter pre-PDD.
Quality of the evidence	Moderate to high quality evidence was identified for sensitivity and specificity and was assessed with the QUADAS tool. Recurrence data was assessed as being of moderate quality using GRADE. The evidence was limited by a lack of long-term follow-up. There were no direct comparisons between PDD and NBI and all patients were initially diagnosed by white light flexible cystoscopy. The evidence suggests enhancement of diagnostic accuracy of WLC by the addition of PDD or NBI but due to the lack of direct comparison it is not known if one is more effective than the other. This prevented the GDG from being able to make a specific recommendation for either PDD or NBI. Therefore, the GDG recommended either PDD or NBI to increase diagnostic accuracy, and also made a research recommendation to compare the two tests. A research recommendation was made because there is no existing comparison of PDD with NBI and it was considered important to ascertain whether either test affects long-term outcomes. The GDG reviewed the data that the use of an initial biomarker might be an effective strategy but using clinical experience they considered that flexible cystoscopy should remain the initial screening investigation in order to diagnose non bladder cancer causes of bladder symptoms. Moderate quality health economic evidence was identified. The evidence was limited by the assumptions about the benefits of detecting bladder cancer earlier. QALYs were not used in the base case analysis, and the economic model did not include NBI. The GDG assumed that NBI would perform similarly to PDD in cost-effectiveness analysis. The cost-effectiveness evidence was used for guidance rather than overriding clinical imperatives.
Trade-off between clinical benefits and harms	The potential benefit of the recommendations is improved diagnostic accuracy of cystoscopy. This may lead to fewer recurrences and therefore fewer TURBTs. This was balanced against the potential harms from more biopsies (some due to false positive findings) leading to increased risk of complications and patient anxiety. There may also be extra catheterisation from an increase in patients undergoing PDD.

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	The GDG agreed that the benefits would outweigh the harms. Improved sensitivity was considered more important for patients than false positives. Improved diagnostic accuracy would also reduce over-treatment resulting from false positive test results.
Trade-off between net health benefits and resource use	The GDG considered the cost-effectiveness evidence presented but this did not override the clinical evidence. The GDG felt that a strategy with flexible cystoscopy as the first line test would always be used, and therefore excluded all strategies that did not include flexible cystoscopy as the initial test. The recommendations may incur costs by the increased use of PDD, NBI or urinary biomarkers as well as the costs associated with more biopsies (including histopathology and morbidity). However, there are potential savings from more accurate diagnosis and the reduction of recurrences and residual tumours. Based on their judgement and the economic evidence presented, the GDG considered that their recommendations were likely to be cost-effective over the long-term. In the economic evidence, the strategy considered to represent current practice was found to be clinically inferior to most other strategies. In a modified analysis for the GDG (where all strategies that did not include flexible cystoscopy as the initial test were excluded), recommended strategies were either dominant (i.e. more effective and less expensive) or had an ICER ranging from £700 to £7,960 per life year gained. Therefore, the recommended approaches are likely to be cost-effective compared to current practice.
Other considerations	No equalities issues were identified for this topic. The GDG considered an impact on current practice because trusts may need to invest in new equipment for all procedures recommended. There may be requirements for investment in new technologies and training, such as urologist training in using PDD and NBI. The GDG were aware that the recommendations form part of a pathway of care and have implications for other recommendations. The GDG are also aware of an ongoing trial in the UK of PDD versus WLC.

Research recommendation	**In people with suspected bladder cancer does using photodynamic diagnosis instead of narrow-band imaging improve outcomes for bladder cancer recurrence, progression or overall survival?**
Why is this important	Both of these technologies have been shown to improve the detection of bladder and in particular aggressive bladder cancer (carcinoma in situ). In principle, this could reduce recurrence and progression, and improve survival. However, there has been no high quality direct comparison between the two technologies in a setting applicable to NHS practice. The question is of high importance, and applicable to thousands of people with bladder cancer across England and Wales. This research might result in the widespread use of photodynamic diagnosis. This would have costs in capacity for staff to deliver it and consumables, but would result in savings through more accurate and quicker diagnosis of bladder cancer, reducing the number of re-resections and other cystoscopies done under general anaesthesia.

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	There is no equality consequence but it would reduce variation in treatment.

3.2 Transurethral surgical technique

The accessibility of the bladder through the urethra (transurethral), means that bladder cancers may be removed by transurethral surgery. There are two main techniques used: transurethral resection or cystoscopy plus biopsy. The vast majority are removed by transurethral resection. Occasional small tumours may be removed more safely by cystoscopy plus biopsy than by transurethral resection due to the lower risk of perforation.

Transurethral resection may involve removing part of or all of the visible cancer. In general all of the visible cancer is removed unless a representative biopsy of an apparently muscle-invasive cancer is deemed appropriate. Representative biopsy would allow confirmation of a muscle invasive cancer that would be treated radically and avoid the risks of transurethral resection of the whole cancer.

Accurate staging of bladder cancer is crucial to discussion of prognosis and treatment options. Staging bladder cancer requires histopathological analysis of a specimen of cancer and associated bladder wall to assess the depth of the cancer. The depth of invasion can only be assessed accurately if all bladder wall layers, including muscle can be examined by the pathologist.

3.2.1 Staging the primary tumour

Despite agreement on the importance of the accuracy of bladder cancer staging, it is not clear how strongly surgical technique during the transurethral resection influences staging and therefore patient outcomes.

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

Clinical evidence (see also full evidence review)

The included evidence is summarised in table 18.

Evidence statement

Three observational studies (972 patients) provided low quality evidence that the risk of recurrence at first follow-up cystoscopy was almost 50% lower for patients where detrusor muscle was present in their TUR specimen compared to those without detrusor muscle in their specimen (RR 0.54, 95% CI 0.46 to 0.64). One randomised trial (Kim *et al.*, 2012) provided very low quality evidence that continuing resection until the presence of muscle in the specimen is confirmed by intra-operative pathology reduces rates of recurrence compared to a grossly complete resection, where only 65% of TUR specimens had muscle present (HR 0.28, 95% CI 0.13 to 0.63). One observational study (28 progression events, 245 patients) provided very low quality evidence that the presence of detrusor muscle in the TURBT specimen was not associated with disease progression after a median follow-up of 20.8 months (p=0.29) (Shoshany *et al.*, 2014). One study (128 patients) reported very low quality evidence that, compared to absence of detrusor muscle, the presence of detrusor muscle at the initial TURBT was associated with lower residual tumour rate at re-TURBT (20.9% versus 51.8%, RR 0.40, 95% CI 0.22 to 0.75) (Huang *et al.*, 2012). No evidence was reported for treatment-related morbidity or health-related quality of life.

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Table 18: GRADE evidence profile: Does the technique of transurethral surgery in new or recurrent bladder cancer influence outcomes. Comparison: TURBT with detrusor muscle versus TURBT without detrusor muscle

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

[1] Mariappan et al. 2010, Mariappan et al. 2012, Roupret et al. 2012 [2] Kim et al. 2012 [3] No intent-to-treat analysis in Kim et al. (2012) [4] 65% of patients in the comparison group had muscle in the TUR specimen. Hazard ratio relates to immediate 2nd TUR until MP present in specimen versus no immediate repeat TUR [5] Low number of events reduces precision [6] Shoshanyet al. 2012 [7] Huang et al. 2012

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Obtain detrusor muscle during TURBT.** **Consider further TURBT within 6 weeks if the first specimen does not include detrusor muscle.**
Relative value placed on the outcomes considered	Recurrence, residual tumour, health-related quality of life, and progression were considered to be the most important outcomes. These outcomes are common events whose frequency is shown to vary with the presence of detrusor muscle. The safety and well-being of patients having TURBT was also considered to be important. Morbidity and health-related quality of life were specified as outcomes in the PICO but were not reported in the evidence. No additional outcomes were used to make recommendations.
Quality of the evidence	The quality of the evidence was very low or low as assessed with GRADE. Risk of bias was identified in the included studies due to observational study design and patient selection for treatments. These issues were taken into account during discussion and the GDG formed a consensus opinion having discussed the evidence. The low quality of the evidence meant that a 'consider' rather than an 'offer' recommendation was made for further resection.
Trade-off between clinical benefits and harms	The potential benefits of the recommendation made include more accurate disease staging at the initial TURBT, which will lead to more informed decision making, efficient and appropriate treatment and reduced recurrence rates. Ensuring the initial TURBT is of the highest quality will improve outcomes for patients and will reduce the need for further resection. The GDG considered that patients without muscle in the initial resection will require further resection which has associated effects on morbidity and quality of life. The GDG also expressed concern about ensuring the safety of resection in certain patient populations, such as patients with thin bladder walls. The GDG considered that the benefits of the recommendations outweighed the risks to a small number of patients who will require a further resection. The GDG also considered that patients' who receive a further TURBT will benefit from having a lower risk of subsequent recurrence.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no health economic model was developed for this topic. The GDG considered that the potential costs from the recommendation arise from the additional TURBTs that will be performed when there is no muscle present in the

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	initial TURBT. This was balanced against the savings from improving the quality of the initial TURBT, which will potentially avoid further TURBTs and the cost associated with disease recurrence and other downstream costs.
Other considerations	No equalities issues were identified for this topic. The GDG believes that the recommendation reflects current best practice and seeks to reduce variation by reinforcing implementation of this best practice. The GDG was unsure how much change in clinical practice is required to achieve universal adherence to this recommendation. The recommendation for further resection within 6 weeks of the initial TUR was based on consistency with the recommendation made in section 4.2.3. The GDG considered the fact that this recommendation does not supersede the requirement for re-resection of high-risk NMIBC, which should take place irrespective of presence of detrusor muscle at initial TURBT.

3.2.2 Assessing normal looking bladder

A few people with bladder cancer will have a separate form where flat patches of aggressive cancer cells involve only the surface lining of the bladder (carcinoma in situ). Carcinoma in situ may produce no visible change in the bladder lining so routine (random) biopsies of normal looking bladder lining have been used to try to detect it in an attempt to improve outcomes.

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

Clinical evidence (see also full evidence review)

The included evidence is summarised in tables 19 and 20.

Evidence statements

One observational study reported very low quality evidence on the recurrence rate at first follow-up cystoscopy (Thortenson *et al.*, 2010). In patients with NMIBC in whom random bladder biopsies were performed (n=260), 40.8% had recurrence at first-follow-up cystoscopy, compared with 21.4% of those who did not undergo random biopsies (n=142). Recurrence rate during a median follow-up of 54 months for those with and without random biopsies was 68.2% and 51.4%, respectively (RR 1.14, 95% CI 0.96 to 1.36) with a trend towards favouring no random biopsies. The rate of positive random biopsies was reported in 11 studies (very low quality evidence) which varied from 4.3% (van der Meijden *et al.*, 1999) to 40% (Librenjak *et al.*, 2010) across studies. Overall 13.6% (580/1420) of random biopsies were positive for pathological findings. The random biopsy procedure varied across studies. For example, Librenjak *et al.* (2010) took biopsies close to the resected tumour edge, whereas most other studies took random biopsies from normal-appearing urothelium at pre-specified sites e.g. bladder neck, trigone, right and left lateral walls, posterior and anterior wall. The studies also varied in the definition of a positive random biopsy, which has an effect on the positive biopsy rate reported (Table 19). The rate of positive biopsies generally increased with increasing stage and grade of the primary tumour. One study (Librenjak *et al.*, 2010) reported that taking biopsy-specimens from normal-appearing urothelium did not prolong the time of resection, neither was it associated with more complications such as

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bleeding and bladder rupture. Progression and health-related quality of life were not reported in the included studies.

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Table 19: Rate of positive random biopsy by study

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

Abbreviations: CIS, carcinoma in situ;

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Table 20: GRADE evidence profile: Does random biopsy, compared to no random biopsy, affect outcomes in people with non-muscle invasive bladder cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Random biopsy	No random biopsy	Relative (95% CI)	Absolute	Quality
Recurrence at first check-up											
1[1]	observational studies	none	none	none	serious[2]	none	104/255 (40.8%)	30/140 (21.4%)	RR 1.44 (1.03 to 2.01)	94 more per 1000 (from 6 more to 216 more)	VERY LOW
Recurrence at first check-up – PUNLMP											
1[1]	observational studies	none	none	none	serious[2]	none	0/10 (0%)	0/24 (0%)	not pooled	not pooled	VERY LOW
Recurrence at first check-up - TaG1-G2											
1[1]	observational studies	none	none	none	serious[2]	none	51/147 (34.7%)	20/95 (21.1%)	RR 1.65 (1.05 to 2.58)	137 more per 1000 (from 11 more to 333 more)	VERY LOW
Recurrence at first check-up - TaG3 and T1G1-G3											
1[1]	observational studies	none	none	none	serious[2]	none	53/98 (54.1%)	10/21 (47.6%)	RR 1.14 (0.7 to 1.84)	67 more per 1000 (from 143 fewer to 400 more)	VERY LOW
Recurrence during follow-up (follow-up median 54 months)											
1[1]	observational studies	none	none	none	serious[2]	none	174/255 (68.2%)	72/140 (51.4%)	RR 1.14 (0.96 to 1.36)	72 more per 1000 (from 21 fewer to 185 more)	VERY LOW
Recurrence during follow-up - PUNLMP (follow-up median 54 months)											
1[1]	observational studies	none	none	none	serious[2]	none	3/10 (30%)	2/24 (8.3%)	RR 3.6 (0.71 to 18.37)	217 more per 1000 (from 24 fewer to 1000 more)	VERY LOW
Recurrence during follow-up - TaG1-G2 (follow-up median 54 months)											
1[1]	observational studies	none	none	none	serious[2]	none	95/147 (64.6%)	56/95 (58.9%)	RR 1.1 (0.89 to 1.35)	59 more per 1000 (from 65 fewer to 206 more)	VERY LOW
Recurrence during follow-up - TaG3 and T1G1-G3 (follow-up median 54 months)											
1[1]	observational studies	none	none	none	serious[2]	none	76/98 (77.6%)	14/21 (66.7%)	RR 1.16 (0.84 to 1.6)	107 more per 1000 (from 107 fewer to 400 more)	VERY LOW
Progression											
0	No evidence available										
Residual tumour rate (assessed with: Positive random biopsy)											
11[3]	observational studies	serious[4]	none	none	none	none	580/4270 (13.6%)	N/A	-	-	VERY LOW
Treatment-related morbidity											
1[5]	observational studies	serious[6]	none	none	serious[2]	none	n=230			R biopsies not associated with more complications e.g.	VERY LOW

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Random biopsy**	**No random biopsy**	**Relative (95% CI)**	**Absolute**	**Quality**
										bleeding	
Health-related quality of life											
0	No evidence available										

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

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Do not take random biopsies of normal-looking urothelium during TURBT unless there is a specific clinical indication (for example, investigation of positive cytology not otherwise explained).**
Relative value placed on the outcomes considered	Health-related quality of life, progression, and recurrence were considered to be the most important outcomes. Recurrence frequency is shown to vary with the presence or absence of random biopsies. The safety and well-being of patients undergoing TURBT was considered important. Progression and quality of life were specified as outcomes in the PICO but were not reported in the evidence. The presence of CIS was not specified as an outcome in the PICO but was considered to be of prognostic importance due to the lack of progression data. If there were data on progression this outcome might not have been considered.
Quality of the evidence	The quality of the evidence was very low as assessed with GRADE. A risk of bias was present in most studies due to the observational study designs and patient selection for random biopsies. These issues were taken into account during discussion and the GDG formed a consensus opinion having discussed the evidence.
Trade-off between clinical benefits and harms	The benefits of the recommendations include potential reduction in unnecessary biopsies and their associated risks. There may be a small reduction of pathology workload, enabling more time to be focused on reporting presence of muscle in the TURBT specimen and muscle invasive disease. The GDG also considered a possible reduction of recurrence due to secondary tumour implantation. The recommendations made may lead to missing occult CIS and therefore underestimating disease risk. The GDG considered that the benefits of the recommendations outweighed the risks to a small number of patients. The available data suggests that harms from avoiding random biopsies are small. The GDG believed that if the recommendations from section 3.1 are followed the theoretical benefits of random biopsies will be further reduced. Therefore the risk of misclassification will be very small and unlikely to have a clinically significant impact
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG considered there to be no costs from the recommendations made. The GDG considered the immediate cost savings from fewer biopsies, shorter time to perform a TURBT and reduced pathology costs.

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	There is also potential avoidance of further recurrence and other downstream costs.
Other considerations	No equality issues were identified. The GDG believes the recommendation reflects current best practice and seeks to reduce variation by reinforcing implementation of this. The GDG also considered recommendations from section 3.1 about the diagnosis of new and recurrent bladder cancer.

3.3 Urinary Biomarkers

For many decades, urine has been examined by cytology to detect bladder cancer cells in people in whom there is a suspicion of bladder cancer. Cytology is moderately good at detecting high grade tumours and much less good at detecting low grade tumours. However, the utility of cytology is dependent on the skill and experience of the cytologist.

Newer non-cytological tests are available and being developed to try to improve upon the utility of urine cytology. Whereas cytology relies on interpretation of the appearance of cells in the urine, the new tests use molecular biological methods to identify cancer cells. The newer tests are not widely used in the NHS at present and are more expensive than urine cytology.

All tests may have false positive results (where the test is positive but there is no cancer) which may occur when there is infection or stone in the kidneys or bladder, following intravesical BCG treatment and after instrumentation of the urinary tract. Tests may also have false negative results (where the test is negative but cancer is present).

It has not been clear at what stage in the diagnostic pathway any of these urine tests might be used, indeed urine tests have been used in combination with other diagnostic modalities. This would depend on the false negative rate (the risk of missing bladder cancer) but also on the false positive rate resulting in unnecessary investigations, anxiety for the person and costs.

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

Clinical evidence (see also full evidence review)

Study quality and results

A Health Technology Assessment (HTA) was identified (Mowatt *et al.*, 2010), which reviewed the diagnostic accuracy of urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology. 83 reports from 71 studies were included in the HTA review. The same exclusion and inclusion criteria used in the HTA were used to guide the literature search for this review question. There were no new studies reporting the test performance of ImmunoCyt. 9 studies were identified relating to NMP22, 9 relating to FISH and 21 reporting the test performance of cytology. Where possible these studies were added to the data from the HTA and pooled analysis was conducted using the bivariate model in accordance with the recommendations of the Cochrane Collaboration.

Evidence statements

A total of 100 studies, reporting the test performance of biomarkers (FISH, ImmunoCyt, NMP22) and cytology in detecting bladder cancer were included in this evidence review. In total, 23 studies enrolling 5735 participants reported on FISH, 10 studies enrolling 4199

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participants reported on ImmunoCyt, 50 studies enrolling 19,190 participants reported on NMP22 and 77 studies enrolling 35,125 participants reported on cytology. Pooled estimates with 95% CIs for sensitivity, specificity, positive and negative likelihood ratios and DORs for each of the tests were undertaken for patient-level analysis. Table 21 shows the pooled estimates for sensitivity, specificity and DOR for each of the tests. Sensitivity was highest for ImmunoCyt at 84% (95% CI 77% to 91%) and lowest for cytology at 46% (95% CI 40% to 52%). ImmunoCyt (84%, 95% CI 77% to 91%) had higher sensitivity than NMP22 (68%, 95% CI 63% to 73%), with the lack of overlap of the CIs supporting evidence of a difference in sensitivity between the tests in favour of ImmunoCyt. FISH (72%, 95% CI 62% to 80%), ImmunoCyt (84%, 95% CI 77% to 91%) and NMP22 (68%, 95% CI 63% to 73%) all had higher sensitivity than cytology (46%, 95% CI 40% to 52%), and again the lack of overlap between the biomarker and cytology CIs supporting evidence of a difference in sensitivity in favour of the biomarkers over cytology. Although sensitivity was highest for ImmunoCyt and lowest for cytology, this situation was reversed for specificity, which was highest for cytology at 95% (95% CI 93% to 96%) and lowest for ImmunoCyt at 75% (95% CI 68% to 83%). Cytology (95%, 95% CI 93% to 96%) had higher specificity than FISH (86%, 95% CI 79% to 90%), ImmunoCyt (75%, 95% CI 68% to 83%) or NMP22 (80%, 95% CI 75% to 84%), with the lack of overlap between the cytology and biomarker CIs supporting evidence of a difference in specificity in favour of cytology over the biomarkers.

Diagnostic odds ratio (DORs) (95% CI) ranged from 9 (6 to 12) to 16 (12 to 23), with higher DORs indicating a better ability of the test to differentiate between those with bladder cancer and those without. Based on the DOR values, ImmunoCyt (16, 95% CI 6 to 26), FISH (15, 95% CI 9 to 27) and cytology (16, 95% CI 12 to 23) performed similarly well and NMP22 relatively poorly (9, 95% CI6 to 12). However, it should be noted that the DOR CIs for each of the tests are fairly wide and all overlap, which limits any firm conclusions that can be drawn from these results. Across studies the median (range) PPV was highest for FISH at 71% (27% to 99%) and cytology at 70% (0% to 100%), followed by ImmunoCyt at 54% (26% to 70%) and NMP22 at 48% (8% to 94%). The median (range) NPV was highest for ImmunoCyt at 93% (86% to 100%), followed by FISH at 87% (36% to 97%), NMP22 at 86% (44% to 100%) and cytology at 83% (27% to 100%). However, predictive values are affected by disease prevalence, which is rarely constant across studies, and therefore these data should be interpreted with caution. There was also heterogeneity across the studies included in the pooled estimates, especially for cytology and FISH. This may be due to the variation in participants across studies (including both those with and without a history of bladder cancer), and the interpretation of the test by the clinician (especially for cytology).

Table 22 summarises the sensitivity of the tests in detecting stage/grade of tumour. ImmunoCyt had the highest median sensitivity across studies (81%) for detection of less aggressive/lower risk tumours whereas FISH had the highest median sensitivity across studies (95%) for detection of more aggressive/higher risk tumours and invasive tumours (90%). For detection of CIS the median sensitivity across studies for both FISH and ImmunoCyt was 100%. Cytology had the lowest sensitivity across studies for detecting less aggressive/lower risk tumours (27%), more aggressive/higher risk tumours (69%), invasive tumours (78%) and also CIS (78%). The median sensitivity across studies for each test was consistently higher for the detection of more aggressive/higher risk tumours than it was for the detection of less aggressive, lower risk tumours. The range of sensitivities across studies for all of the tests was very wide and therefore some caution is warranted when interpreting these results.

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Table 21: Summary of pooled estimate results for biomarkers and cytology for patient-based detection of bladder cancer

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

Table 22: Summary of median (range) sensitivity of tests across studies for patient-level detection of stage/grade of bladder cancer

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

[a] *The number of patients refers to the number included in the overall analysis by the studies*

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Cost-effectiveness evidence

The primary results of the analysis by Mowatt et al. 2010 are summarised in the table 23. While the study is of methodologically high quality, there were concerns about the use of life years as the primary effectiveness measure in the majority of analyses. This makes cost-effectiveness difficult to assess as there is no established cost-effectiveness threshold based on life years in the UK.

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

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

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

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

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

Overall, it is difficult to fully and robustly assess cost-effectiveness in this area. However, it does appear that strategies involving urinary biomarkers, cytology or PDD provide additional benefits compared to current practice and do so at a cost that society might be willing to pay. Of particular note to the topic at hand is that the urinary biomarkers; FISH and Immunocyt may be cost-effective alternatives to the investigations used in current practice.

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Table 23: Modified GRADE table showing the included evidence (Mowatt et al. 2010) comparing urine tests and endoscopic techniques in the diagnosis of new and recurrent bladder cancer

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

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Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		12. CSC_CTL_PDD (CTL_WLC)	£1,859	11.65 LYs	£401	0	Dominated	Throughout the analyses, one of the following strategies was the most cost-effective strategy (assuming a threshold of £30,000 per life year): CTL_WLC (CTL_WLC) CTL_PDD (CTL_PDD) IMM_PDD (IMM_WLC) FISH_PDD (FISH_WLC) CSC_FISH_PDD (FISH_WLC) CSC_PDD (CSC_WLC) CSC_IMM_PDD (IMM_WLC) Probabilistic sensitivity analyses In addition, a probabilistic sensitivity analysis (PSA) was conducted for both the base case analysis and the sensitivity analysis where QALYs are		
		13. CSC_WLC (CSC_WLC)	£1,920	11.60 LYs	£462	-0.04	Dominated			
		14. CSC_IMM_WLC (IMM_WLC)	£1,941	11.63 LYs	£483	-0.02	Dominated			
		15. CSC_CTL_WLC (CSC_WLC)	£1,997	11.62 LYs	£539	-0.03	Dominated			
		16. CSC_FISH_PDD (FISH_WLC)	£2,005	11.66 LYs	£547	0.01	£60,284			
		17. CSC_FISH_WLC (CSC_WLC)	£2,042	11.63 LYs	£37	-0.03	Dominated			
		18. CSC_NMP22_WLC (CSC_WLC)	£2,070	11.62 LYs	£65	-0.03	Dominated			
		19. CSC_PDD (CSC_WLC)	£2,082	11.63 LYs	£77	-0.03	Dominated			
		20. CSC_NMP22_PDD (NMP22_WLC)	£2,089	11.65 LYs	£84	-0.01	Dominated			
		21. CSC_IMM_WLC (CSC_WLC)	£2,105	11.63 LYs	£100	-0.03	Dominated			
		22.CSC_CTL_PDD (CSC_WLC)	£2,145	11.64 LYs	£140	-0.01	Dominated			
		23. CSC_IMM_PDD (IMM_WLC)	£2,195	11.66 LYs	£190	<0.01	£309,256			

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Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		24. CSC_FISH_PDD (CSC_WLC)	£2,270	11.66 LYs	£75	0	Dominated	used. In both analyses, the PSA results demonstrated considerable uncertainty. Indeed, there was no clear strategy that would be preferred based on the PSA results. However, in the analysis using QALYs, three strategies were found to have around a 20% probability of being cost-effective over much of the thresholds; CTL-WLC (CTL-WLC), FISH-PDD (FISH-WLC) and CSC-FISH-WLC (FISH-WLC).		
		25. CSC_NMP22_PDD (CSC_WLC)	£2,318	11.65 LYs	£123	-0.01	Dominated			
		26. CSC_IMM_PDD (CSC_WLC)	£2,370	11.65 LYs	£175	<0.01	£237,863			
		Base case analysis results without dominated and extendedly dominated options (using LYs as effectiveness measure)								
		1. CTL_WLC (CTL_WLC)	£1,043	11.59 LYs	-					
		2. CTL_PDD (CTL_WLC)	£1,094	11.60 LYs	£51	0.01	£3,423			
		4. FISH_PDD (FISH_WLC)	£1,235	11.64 LYs	£141	0.04	£3,806			
		8. IMM_PDD (IMM_WLC)	£1,458	11.65 LYs	£223	0.01	£28,864			
		16. CSC_FISH_PDD (FISH_WLC)	£2,005	11.66 LYs	£547	0.01	£60,284			
		26. CSC_IMM_PDD (CSC_WLC)	£2,370	11.65 LYs	£365	<0.01	£270,375			
		Sensitivity analysis using quality adjusted life years [QALYs] as effectiveness measure								
		1. CTL_WLC (CTL_WLC)	£1,043	9.00 QALYs	-					
		2. CTL_PDD (CTL_WLC)	£1,094	9.01 QALYs	£51	0.01	£4,678			
		4. FISH_PDD	£1,235	9.04	£141	0.03	£5,051			

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Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		(FISH_WLC)		QALYs						
		8. IMM_PDD (IMM_WLC)	£1,458	9.04 QALYs	£223	<0.01	Extendedly dominated			
		16. CSC_FISH_PDD (FISH_WLC)	£2,005	9.05 QALYs	£770	0.01	£66,905			
		19. CSC_PDD (CSC_WLC)	£2,082	9.01 QALYs	£77	-0.04	Dominated			
		23. CSC_IMM_PDD (IMM_WLC)	£2,195	9.05 QALYs	£190	0	Dominated			
		26. CSC_IMM_PDD (CSC_WLC)	£2,370	9.05 QALYs	£365	0	Dominated			
	Comments: The majority of the analyses use life years as the measure of the effectiveness. Quality adjusted life years (QALYs) are the preferred effectiveness measure of NICE.									

Abbreviations and notation:

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

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

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

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

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Recommendations	**Do not substitute urinary biomarkers for cystoscopy to investigate suspected bladder cancer or for follow-up after treatment for bladder cancer, except in the context of a clinical research study.** **Do not use urinary biomarkers or cytology in addition to cystoscopy for follow-up after treatment for low-risk bladder cancer.**
Relative value placed on the outcomes considered	All outcomes from the PICO were reported in the evidence. No additional outcomes were used to make recommendations. Sensitivity was considered to be the most important outcome by the GDG as it is important not to miss significant disease. Specificity was looked at but considered not to be the most important outcome when making the recommendations.
Quality of the evidence	The quality of evidence for diagnostic accuracy was assessed using the QUADAS tool and was considered to be of good quality. No major issues with the evidence were presented. There was heterogeneity across the studies included in the pooled estimates, especially for cytology and FISH, which may be due to the variation in participants across studies (including both those with and without a history of bladder cancer), and the interpretation of the test by the clinician (especially for cytology). Two research recommendations were made because there was limited data on the clinical impact of using biomarkers, which have a lower sensitivity then cystoscopy despite being cost-effective. There is also an absence of longitudinal data on patients who were followed up using biomarkers only. There is also uncertainty about the value of adding biomarkers to cystoscopic follow-up in patients with high risk bladder cancer who have been treated with BCG. The GDG considered that there was not enough evidence to change current practice and hence made 'do not use' recommendations. The research recommendations were set out to try and obtain evidence to inform future practice. Moderate quality cost-effectiveness data was identified. The evidence was limited by the assumptions about the benefits of detecting bladder cancer earlier and that QALYs were not use in the base case analysis. This meant that the GDG used the cost-effectiveness evidence for guidance rather than overriding clinical evidence.
Trade-off between clinical benefits and harms	The GDG considered the main benefits of the recommendations to be a reduction in missed diagnosis and avoiding unproven and expensive tests in low-risk disease. The potential harms of the recommendations include the missed opportunity to reduce cystoscopy use. The recommendations may delay the detection of progression, so progression rates could increase. However, the GDG considered that this would affect a very small proportion of patients. Identification of tumours was prioritised by the GDG over the potential harm and expense of cystoscopy.
Trade-off between net health benefits and resource use	A published health economic model was presented but this did not override the clinical evidence. The GDG considered that the recommendations would incur some savings from reduced use of cytology and biomarkers for the follow-up of

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	low-risk non-muscle invasive bladder cancer The GDG considered that no additional costs would be incurred from the recommendations made as they are not in addition to standard treatment.
Other considerations	No equalities issues were identified for this topic. The GDG considered that there may be a reduction in the use of biomarkers in patients with bladder cancer and a reduction in the use of cytology in patients with low-risk disease. The GDG also considered the impact of previous BCG treatment on the use of cytology and PDD during patient follow-up. The implications of methods of diagnosis were considered separately for new patients and patients undergoing follow-up and those with high or low risk disease. The evidence presented in the HTA was stratified by these subgroups, therefore the GDG were able to make specific recommendations for these subgroups. For example, cytology had lower sensitivity than other tests for low-risk disease.

Research recommendation	**Do biomarkers or novel cystoscopic technologies improve outcomes in patients undergoing surveillance after a diagnosis of bladder cancer compared to standard cystoscopic surveillance? Outcomes of interest are HRQoL, progression to MIBC, cystectomy rate, and bladder cancer mortality.**
Why is this important	In people with high risk bladder cancer, the use of cytology or FISH as an adjunct to follow-up cystoscopy may improve cancer detection rates. However, there is little contemporary comparative data, there is variation between investigated cohorts and that not all progressing cancers are found using current biomarkers. Thus, whilst the addition of cytology or FISH may allow the safe reduction in the frequency of cystoscopy, some people with bladder cancer may be disadvantaged by this approach. Further research is needed to assess current biomarkers in the follow-up of bladder cancer to determine whether their use can safely allow a reduction in the frequency of follow-up cystoscopy, and to find novel markers with better performance for identifying disease progression.

Research recommendation	**Does the addition of biomarkers or cytology to cystoscopy improve outcomes in patients undergoing surveillance after receiving BCG therapy for bladder cancer? Outcomes of interest are HRQoL, progression to MIBC, cystectomy, and bladder cancer death**
Why is this important	People with high risk NMIBC are usually followed by cystoscopic surveillance. Cystoscopy is intrusive, uncomfortable for patients and costly. Cystoscopy may also miss significant lesions (sensitivity 71%, sensitivity 72%). Several tests (eg cytology, NMP22, FISH) have been reported to be able to detect recurrent bladder cancer. They have low sensitivity for low grade disease but high sensitivity for high grade disease (e.g FISH sensitivity 72%, Specificity 86%). In a HTA assessment (Mowatt et al 2010) and an analysis for this guideline strategies of using these tests alongside or instead of cystoscopy were shown to be more effective and less costly than current models of care. They were not recommended as the results have been inferred from models rather that directly studied with no direct clinical comparisons of the outcomes of using these approaches. This research proposal seeks to obtain this evidence.

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3.4 Imaging

Imaging is used to assess the extent of disease in people with bladder cancer, to inform discussions about prognosis and treatment options. Imaging can provide more information about the presence or absence of cancer in:

- the muscle wall of the bladder (or through it)
- pelvic lymph nodes
- the abdomen including the upper urinary tracts (kidneys and ureters)
- the chest
- the bones

The likelihood of spread beyond the bladder is very low in people with non-muscle invasive bladder cancer but high in people with muscle invasive bladder cancer.

Several imaging techniques are available and are used to varying degrees across the NHS. These include:

- plain X-ray
- ultrasound
- IVU
- CT
- MRI
- PET CT
- Bone scintigraphy

The different imaging techniques vary in their suitability for identifying and providing detail about normal anatomical structures and disease processes. There is also variation in the costs of the different technologies and the expertise required for their use. Local use depends on these factors as well as local or regional policy. In general, plain X-ray and ultrasound are well tolerated. Techniques that use intravenous contrast (IVU, CT and MRI) have some risk of allergy and of renal injury in those with renal impairment. MRI can be very noisy and can precipitate claustrophobia.

3.4.1 Staging of the bladder and pelvic lymph nodes

For staging of the bladder and pelvic lymph nodes, CT is used most commonly in the NHS, with MRI used instead or as well in some centres. Ultrasound can examine the bladder wall but this is seldom used for local staging. CT is quicker, cheaper and more widely available than MRI. Newer MRI techniques such as dynamic perfusion and diffusion-weighted imaging, may give more detailed images and functional information compared to CT. 18F-FDG-PET/CT can be used for pelvic lymph node staging but is not widely available.

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

Clinical evidence (see also full evidence review)

The included evidence is summarised in tables 24 and 25.

Study quality and results

The QUADAS-2 assessment tool was used to evaluate risk of bias in the 36 diagnostic accuracy studies. The evidence was assessed as being of moderate quality. A majority of

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studies had a low risk of patient selection bias, as they recruited a consecutive or random sample of patients and avoided inappropriate exclusions. Most studies also reported that the index test (imaging) results were interpreted without knowledge of the reference standard (histopathology of surgical specimens or clinical/radiological follow-up) and reported diagnostic criteria. However, most studies did not report whether the reference standard was interpreted without knowledge of the index test results. 61% of studies were at low risk of 'flow and timing' bias. Some studies were classified as being at unclear or high risk as they did not report the interval between imaging and the reference standard, and in some studies not all patients received the same reference standard (e.g. cystectomy or TURBT). Data were not pooled due to heterogeneity in the reported outcomes.

Evidence statements

Staging accuracy

37 studies were identified and included in the evidence review. 36 studies reported the staging accuracy of CT, MRI or PET-CT. One study reported on the effect of PET-CT on the management of patients with muscle-invasive bladder cancer or high grade T1 bladder cancer. 18 studies provided data about the staging accuracy of CT and/or MRI (Table 24). Four studies reported staging accuracy for both CT and MRI (Tachibana et al., 1991; Kim et al., 1994; Tanimoto et al., 1992; Vargas et al., 2012). Three of these studies reported more accurate T-staging with MRI, and one study of 16 patients reported no significant difference between CT and MRI (Vargas et al., 2012). Across 28 studies (with approximately 1365 patients), the staging accuracy of MRI ranged from 30% to 89%. Across five studies (with approximately 471 patients), the staging accuracy of CT ranged from 45% to 63%.

Sensitivity and specificity for T2 or higher

29 studies reported the sensitivity and specificity of the imaging modalities for detecting metastatic lymph nodes, or for distinguishing muscle invasive from non-muscle invasive bladder cancer (Table 25). Tachibana et al. (1991) reported the sensitivity and specificity for classifying the presence or absence of muscle invasion in 57 patients (31 of whom had NMIBC) was 96% and 58% respectively for CT and 96% and 83% for enhanced MRI. Specificity was significantly higher with MRI. Takeuchi et al. (2009) reported tumour-based analysis of MRI for detecting Tis-T1 tumours from T2-T4 tumours in 40 patients (23 with NMIBC). Specificity with T2WI plus DWI (100%) or all three image types together (100%) were better than that obtained with T2WI alone (74%). Sensitivity was not improved when DWI was used, with sensitivity of 88% for both T2WI and T2WI plus DWI and 94% for T2WI plus contrast enhancement. Six MRI studies (590 patients) reported patient-based analysis of sensitivity and specificity. The proportion of patients with muscle invasive bladder cancer ranged from 17% to 54% across these studies. Sensitivity ranged from 68% to 100%, and specificity ranged from 73% to 92%. Data were not pooled due to heterogeneity across studies.

Sensitivity and specificity for T3b or higher

Kim et al. (1994) reported that when 36 patients were grouped as Ta-T3a and T3b-T4, the sensitivity and specificity for staging was 93% and 71% for CT and 86% and 73% for dynamic enhanced MRI. There were no significant differences in sensitivity and specificity between CT and MRI or between any of the MRI techniques (e.g. T1WI, T2WI, dynamic enhanced imaging and late enhanced imaging). Two CT studies with 167 patients in total reported the accuracy of detecting perivesical invasion (Kim et al. 2004; Baltaci et al. 2008). The sensitivity and specificity was 89% and 95% in Kim et al. (2004) and 85% and 63% in Baltaci et al. (2008). Five MRI studies (736 patients) reported the diagnostic accuracy of distinguishing T2 or lower from T3 or higher bladder cancer (Daneshmand et al., 2012; Rajesh et al., 2011; Tekes et al., 2005; Wu et al., 2013; Ghafoori 2013). Sensitivity ranged from 77% to 93% and specificity ranged from 60% to 95% across studies.

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Sensitivity and specificity for regional lymph node metastases

Data were not pooled due to heterogeneity across studies. The prevalence of metastatic pelvic lymph nodes varied across studies, which could be caused by variations in patient populations or variation in the number of lymph nodes removed at surgery. The prevalence of metastatic lymph nodes ranged from 17% to 53% in the five FDG PET-CT studies (n=206), from 13% to 45% across the eight CT studies (n=542) and from 13% to 33% across the seven MRI studies (n=355). For FDG PET-CT, sensitivity ranged from 33% to 70% and specificity ranged from 87% to 100% across five studies. For CT, sensitivity ranged from 9% to 75% and specificity ranged from 56% to 100% across eight studies. For MRI, sensitivity ranged from 0% to 86% and specificity ranged from 71% to 100% across seven studies. Two studies reported the detection of metastatic lymph nodes with C-choline PET-CT with sensitivity of 58% and 63% and specificity of 66% and 100% reported by Maurer et al. (2012) and Picchio et al (2006) respectively. One study reported node-based detection of DW contrast enhanced MRI with a sensitivity of 76% and specificity of 89% (Papalia et al. 2012). Deserno et al. (2004) reported node-based detection in 172 nodes with Ferumoxtran-10 MRI. The pre-contrast and post-contrast sensitivities were 76% and 96% respectively. The pre-contrast and post-contrast specificities were 97% and 95%, respectively. Schoder et al. (2012) reported nodal-based detection for C-acetate PET-CT, with sensitivity of 100% and specificity of 87%.

Change in management

Mertens et al. (2013) compared treatment decisions before and after PET-CT. In 96 patients PET-CT was performed after conventional staging with CT scans of the abdomen and chest. PET-CT upstaged 20% of patients. Treatment recommendations changed in 13/96 (13.5%) patients after PET-CT imaging. Treatment changed in 6/47 patients from direct cystectomy to neoadjuvant chemotherapy based on additional lesions seen at PET-CT. All lesions were confirmed by fine-needle aspiration. 7/82 patients changed from curative treatment to palliative management. Five patients did not follow post-FDG-PET treatment due to poor performance status, comorbidities or refusal of therapy.

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Table 24: Accuracy of T-staging by imaging modality (% of tumours understaged, overstaged and accurately staged by imaging)

Study	Total N patients	Ref standard (N)	Type of CT	N CT stage / N Pathological stage						No. (%) under-staged	No. (%) over-staged	No. (%) accurately staged	Type of MRI	N MRI stage / N Pathological stage						No. (%) under-staged	No. (%) over-staged	No. (%) accurately staged
				Ta	T1	T2	T3a	T3b	T4					Ta	T1	T2	T3a	T3b	T4			
Tachibana et al. 1991	57	TUR (26)	CECT	13/26						7 not detected	6 (23)	13 (50)	Gd-CE	22/26						1 not detected	4 (15)	22 (85)
		RC (31)		1/5		5/11	2/6	5/7	1/2	6 (19)	10 (32)	14 (45)[1]		3/5		7/11	4/6	4/7	2/2	5 (16)	6 (19)	20 (65)
Kim et al. 1994	36	TUR (14) RC (22)	CECT	0/3		3/7	0/2	10/12	3/4	3 (10)	10 (34)	16/29 (55)	T1W	0/3		0/9	2/4	9/12	5/6	8 (22)	12 (33)	16 (44)
													T2W	1/3		4/9	2/4	10/12	5/6	5 (14)	9 (25)	22 (61)
													Gd-CE	1/3		3/6	1/2	9/10	4/4	2 (7)	7 (26)	18(67)
													Late Gd-CE	1/3		3/9	2/4	10/12	6/6	1 (3)	12 (33)	23 (64)
Tanimoto et al. 1992	86 tumour	TUR (47) RC (32)	CECT	26/54		5/9	3/6	8/11	5/6	5 (6)	23 (27)	47 (55)[2]	Gd-CE	33/54		8/9	4/6	10/11	6/6	3 (3)	5 (6)	73 (85)[3]
													Conventional MRI	33/54		2/9	3/6	7/11	5/6	9 (10)	18 (21)	50 (58)[4]
Vargas et al. 2012	16	All RC	CECT	-		-	-	-	-	1 (6)	5 (31)	10 (63)	Gd-CE	-		-	-	-	-	1 (6)	6 (38)	9 (56)
Tritschler et al. 2012a	276	RC	MDCT	63/114				29/96	18/46	30%	17%	51%										
Rajesh et al. 2011	100	All TUR											Gd-CE phased array body coil	32/55		28/40	-	2/3	1/2	13 (13)	24 (24)	63 (63)
Daneshmand et al. 2012	122	All RC											Dynamic Gd-CE	T02/14	4/28	23/38	12/27		8/15	29 (27)	31 (29)	47 (44)
Tekes et al. 2005	71	Unclear											Gd-CE phased array pelvic coil	16/24		6/10	11/21		7/6	4 (6)	23 (32)	44 (62)
Neuerberg et al. 1991	68	TUR (47)											Gd-CE	6/31		5/11		5/6	8/9	14 (25)	19 (33)	24 (42)
	26	RC (13) Biopsy											T1W+T2W	0/13		1/3		3/3	3/4	5 (22)	11 (48)	7 (30)

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

Study	Total N patients	Ref standard (N)	Type of CT	N CT stage / N Pathological stage						No. (%) under-staged	No. (%) over-staged	No. (%) accurately staged	Type of MRI	N MRI stage / N Pathological stage						No. (%) under-staged	No. (%) over-staged	No. (%) accurately staged
				Ta	T1	T2	T3a	T3b	T4					Ta	T1	T2	T3a	T3b	T4			
																		11			(17)	
													Late Gd-CE	11/25		-	5/9	10/11	1/1	1 (2)	20 (42)	27 (56)

RC, radical cystectomy; TUR, transurethral resection; CE CT, contrast-enhanced CT; NR, not reported; Gd-CE, Gadolinium-contrast enhanced MRI; MDCT, Multi-detector CT;
[1] 1 pT2 tumour not detected by CT; [2] 11 pT1 tumours not detected by CT; [3] 5 pT1 tumours not detected by Gd-CE MRI; [4] 9 pT1 not detected by conventional MRI

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Table 25: T staging and Lymph node (LN) staging sensitivity and specificity

Study	Total N patients	Outcome	Pathology staging (No. pN+)	Type of CT	CT staging (%)				Type of MRI	MRI staging (%)			
					Sensitivity	Specificity	PPV	NPV		Sensitivity	Specificity	PPV	NPV
Tachibana et al. 1991	57	≤T1 versus ≥T2	31 RC, 26 TUR	CE CT	96	58	71	93	Gd-CE	96	83	83	96
Kim et al. 1994	36	Ta-T3a versus T3b-T4	22 RC, 14 TUR	CE CT	93	71	78	91	T1W	78	78	78	78
									T2W	83	78	79	82
									Gd-CE	86	73	80	80
									Late Gd-CE	86	100	72	78
Jensen et al. 2011	18	LN detection	RC (3)	F-FDG PET/CT	33	93	50	88	T1+T2	0	80	0	80
Liedberg et al. 2013	47	≤T2 versus ≥T3 or N+	RC (8)	CE CT	86	42	55	79	3-T enhanced T1 and T2	86	31	50	73
		LN detection								50	90	50	90
Vargas et al. 2012	16	LN detection	RC (2)	CT	50	79	25	92	Gd-CE phased array body coil	50	71	20	91
				C-acetate PET/CT	100	71	33	100					
Daneshmand et al. 2012	122	LN detection	RC (27)						Gd-CE	41	87	48	84
		≤T2N0 versus ≥T3N0								77	60	76	61
Takeuchi et al. 2009	40 (52 tumours)	≤T1 versus ≥T2	17 RC 23 TUR						T2 weighted	88	74	63	93
									T2 plus DW	88	100	100	95
									T2 plus CE	94	86	76	97
									All image sets	94	100	100	97
		≤T2 versus ≥T3							T2 weighted	50	95	71	88
									T2 plus DW	70	97	88	93
									T2 plus CE	80	92	88	93
									All image sets	80	97	89	95
Rajesh et al. 2011	100	≤T1 versus ≥T2	TUR						Gd-CE phased array body coil	78	93	94	78
		≤T2 versus ≥T3								91	60	98	25
Tekes et al. 2005	62	≤T1 versus ≥T2	RC (10)						1.5-T GDE	97	67	77	96
		≤T2b versus ≥T3								86	84	77	90
		LN detection								70	98	88	95
Wu et al. 2013	362	≤T1 versus ≥T2	NR						3-T T2W	87	73	57	93
									DW	89	91	80	95
									T2W+DW	92	98	95	97
	344	≤T2 versus ≥T3	RC						3-T T2W	81	91	67	96
									DW	85	95	79	97
									T2W+DW	89	97	87	98
Rosenkratz et al. 2012	23	≤T1 versus ≥T2	16 Biopsy 7 RC						T2W	100	79	50	100
Kobayashi et al.	104	≤T1 versus ≥T2	TUR						DWI	66	91	81	82

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Study	Total N patients	Outcome	Pathology staging (No. pN+)	Type of CT	CT staging (%)				Type of MRI	MRI staging (%)			
					Sensitivity	Specificity	PPV	NPV		Sensitivity	Specificity	PPV	NPV
2011									T2WI	68	91	81	83
Barentsz et al. 1996	57	LN detection	RC (14)						Unenhanced T1+T2	71	98	91	91
									Unenhanced T1+T2+DWI	86	95	86	95
Ghafoori et al. 2013	108 (tumours)	≤T1 versus ≥T2	10 TUR 76 RC						T1+T2 contrast enhanced	98	82	98	82
		≤T2 versus ≥T3								93	94	94	93
Papalia eta l. 2012	72 (nodes)	LN detection	RC (34)						DWI GDE	76	89	87	71
Watanbe et al. 2009	19	≥T2	10 TUR, 8 RC						T1+T2	80	79	57	92
									T1+T2+GDE	80	79	57	92
									T1+T2+DWI	40	93	67	81
Deserno et al. 2004	172 (nodes)	LN detection	PLND (50)						Ferumoxtran-10 MRI - precontrast	76	97	97	91
									Ferumoxtran-10 MRI - postcontrast	96	95	89	98
Maeda et al. 1995	26	≤T1 versus ≥T2	17 TUR 9 RC						0.5-T Unenhanced T1+T2	100	92	93	100
Persad et al. 1993	24	LN detection	RC (5)						0.5-T Unenhanced T1+T2	63	100	100	84
Swinnen et al. 2010	51	LN detection	RC (13)	CT	46	92	67	83					
				F-FDG PET/CT	46	97	86	84					
Picchio et al. 2006	27	LN detection	RC (8)	CE CT	50	68	40	76					
				C-choline PET/CT	63	100	100	86					
Maurer et al. 2012	44	LN detection	RC (12)	CE CT	75	56	39	86					
				C-choline PET/CT	58	66	39	81					
Kim et al. 2004	67	Diagnosing perivesical invasion	RC	Dynamic CE CT	89	95	83	96					
Lodde et al. 2010	44	LN detection	RC (13)	CE CT (n=33)	33	100	100	64					
				F-FDG PET/CT (n=44)	57	100	100	67					
Hitier-Berthault et al. 2013	52	LN detection	RC (22)	CT	9	90	40	57					
				F-FDG PET/CT	36	87	67	65					
Tritschler 2012	243	LN detection	RC (72)	CT	30	90	58	74					

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Study	Total N patients	Outcome	Pathology staging (No. pN+)	Type of CT	CT staging (%)				Type of MRI	MRI staging (%)			
					Sensitivity	Specificity	PPV	NPV		Sensitivity	Specificity	PPV	NPV
Baltaci et al. 2008	100	LN detection	RC (13)	CT	31	94	44	90					
		Perivesical invasion			85	63	61	86					
Schoder et al. 2012	109 (nodes)	LN detection	RC (3)	C-acetate PET/CT	100	87	18	100					
Kibel et al. 2009	41	LN detection	RC (10)	FDG PET/CT	70	94	78	91					

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

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider CT or MRI staging before transurethral resection of bladder tumour (TURBT) if muscle-invasive bladder cancer is suspected at cystoscopy.** **Offer CT or MRI staging to people diagnosed with muscle-invasive bladder cancer or high-risk non-muscle-invasive bladder cancer that is being assessed for radical treatment.** **Consider fluorodeoxyglucose positron emission tomography (FDG PET)-CT for people with muscle-invasive bladder cancer or high-risk non-muscle-invasive bladder cancer before radical treatment if there are indeterminate findings on CT or MRI, or a high risk of metastatic disease (for example T3b disease).**
Relative value placed on the outcomes considered	Sensitivity and specificity for stage T3b or higher disease, T2 or higher disease, local recurrence, and regional lymph node metastasis was considered to be important outcomes because accurate staging is important in management decision-making for bladder cancer. Change in management was also considered to be an important outcome because it can affect patient outcomes. Overall survival, progression-free survival, and morbidity associated with the procedure were specified as outcomes in the PICO but were not reported in the evidence. No further outcomes were used when making the recommendations.
Quality of the evidence	The evidence was assessed as being of moderate quality using the QUADAS-2 tool. The evidence was limited by a lack of comparative data and by consisting of many retrospective cohort studies and older studies that may not reflect the imaging techniques used in current practice. There were also limitations from small sample sizes in the included studies. The duration between the index test and the gold standard was not reported in some studies. Pre-or post TURBT imaging was also not always clearly reported and some imaging was performed after TURBT. Some studies were limited by a lack of histological gold standard and the standard varied within and between studies. It was also unclear in many studies whether the interpretation of the reference standard was blinded to the index test result. Heterogeneity in the reported outcomes prevented pooling of the data. These limitations affected the strength of the recommendation that could be made, and a ‘consider’ rather than an ‘offer’ recommendation was made. Due to the lack of high quality evidence, the GDG could not recommend one type of imaging (CT or MRI) over the other. The recommendation to perform imaging before TURBT was partially

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	based on the GDG's clinical experience. This issue was discussed within the studies included in the evidence review, but was not directly assessed by any of the studies. No health economic evidence was identified.
Trade-off between clinical benefits and harms	The GDG considered the potential benefits of the recommendations made to be standardised imaging across the country, improved timing and accuracy of the diagnostic pathway, and increased access to PET imaging for bladder cancer patients. The GDG considered that accurate staging will lead to better targeted treatment and less inappropriate treatment. These clinical benefits were balanced against the potential harm from increased radiation exposure in a small number of patients having additional PET imaging. The GDG also considered that there may be a possible increase in imaging in a small number of patients who don't have high risk disease. The GDG considered that a shorter, more efficient diagnostic pathway and increased accuracy of staging will outweigh the potential minor harm to a small number of patients.
Trade-off between net health benefits and resource use	No health economic model was developed for this topic. However, the GDG considered the potential costs of the recommendations to result from increased imaging in bladder cancer patients, particularly increased CT and PET-CT. These costs were balanced against the potential savings resulting from less inappropriate radical treatment. The GDG considered that a more streamlined pathway will reduce costs. However, the GDG were unsure if there would be net cost savings from the recommendations made.
Other considerations	The GDG considered a potential change in practice will result from increased access to PET-CT for bladder cancer patients. There may also be significant changes in the current diagnostic pathway from these recommendations, especially to facilitate imaging before TURBT. The GDG considered it important to produce a coherent pathway from the different topics and evidence reviews in the guideline. The GDG were concerned about the current length of diagnostic pathways for bladder cancer patients and were keen to minimise that pathway and to perform CT earlier in the pathway. The GDG considered the overlap between the review questions in section 3.4 and wanted to ensure that any imaging and combination of imaging was done most effectively. They also considered that CT urography may have been performed earlier in the diagnostic pathway as an investigation of haematuria.

3.4.2 Detecting upper urinary tract involvement

The upper urinary tracts can be assessed for cancer using ultrasound, IVU, CT or MRI. In the NHS, IVU and CT are used most often. CT gives more detail but is more costly and may be less readily available. CT also shows detail of the entire area examined whereas an IVU gives much less information about structures outside the urinary tract. For people with

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bladder cancer, therefore, CT of the abdomen will allow detection of spread outside the urinary tract, for example to the liver.

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

Clinical evidence (see also full evidence review)

The evidence is summarised in table 26 and 27.

Study quality and results

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

Evidence statements

*Sensitivity and specificity for presence of tumour in upper tract*Three studies reported the diagnostic accuracy of multi-detector CT urography for the detection of tumour in the upper tract, with sensitivity ranging from 88% to 100% and specificity ranging from 91% to 95% (see table 26). One study of 104 patients also reported the diagnostic accuracy of excretory urography for the detection of tumour in the upper tract, with sensitivity of 80% and specificity of 81% (Jinzaki et al., 2011). This study reported that sensitivity and specificity of CT urography was significantly greater than excretory urography.

The proportion of upper tract tumours detected by intravenous urography/CT urography is shown in table 27. Three low quality studies (1340 patients) reported the incidence of upper urothelial tract tumours at diagnosis of bladder cancer, which ranged from 0.3% to 1.7% across studies. Herranz-Amo et al. (1999) reported that intravenous urography (IVU) detected six out of the nine (67%) upper tract tumours. Three low quality studies reported the incidence of upper tract tumours during follow-up of bladder cancer. In Hession et al. (1999) 3.4% of patients developed an upper tract tumour, all of which were detected on IVU but there were also two false positive cases. Miyake et al. (2006) reported that 20 (4.6%) patients developed an upper tract tumour during follow-up, two of which were detected by routine IVU and 18 of which presented with symptoms that initiated extra IVU. Meissner et al. (2007) reported on 322 patients undergoing follow-up after radical cystectomy. 15 (4.7%) developed an upper tract tumour, eight of which were detected by routine IVU. One study (Shinagare et al., 2013) reported on 105 patients undergoing CT urogram for follow-up after radical cystectomy. Three (2.9%) patients developed an upper tract tumour.

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

Table 26: Patient-level sensitivity and specificity for presence of tumour in upper urinary tract

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

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Table 27: Incidence of upper urothelial tract tumours and proportion detected by intravenous urography/CT urography

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

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider CT urography, carried out with other planned CT imaging if possible, to detect upper tract involvement in people with new or recurrent high-risk non-muscle-invasive or muscle-invasive bladder cancer.**
Relative value placed on the outcomes considered	Sensitivity and specificity were considered by the GDG to be the most important outcomes because accurate detection of upper tract cancer is an important diagnosis to make and can affect management of the disease. It is also a surrogate for other outcomes. The outcomes of change in management, overall survival, progression-free survival, and morbidity associated with the procedure were specified in the PICO but were not reported in the evidence. The outcome of incidence of upper urinary tract tumours was not specified in the PICO but was considered by the GDG when making the recommendation. The GDG considered that there was a low incidence of upper tract tumours in low risk disease. The GDG based the recommendation on the balance between the number of patients needed to be tested in order to identify an upper tract tumour.
Quality of the evidence	The evidence was assessed as being of low quality using the QUADAS-2 tool. The main limitation of the evidence was a lack of high quality comparative studies. Some of the presented studies included a variety of patients that were not relevant to the review question as they did not all have newly diagnosed or recurrent bladder cancer. A majority of the studies were retrospective. Also the low incidence of upper urinary tract tumours limited the conclusions that could be drawn from the evidence. These limitations affected the strength of the recommendation. A 'consider' rather than an 'offer' recommendation was made. The GDG were unable to make a strong statement about imaging in low risk disease or whether upper tract imaging can be omitted in low risk groups. There was no evidence about whether or not upper tract imaging is useful for low risk disease. Therefore, part of the recommendation was based on the GDG's clinical experience that upper tract tumours are relatively uncommon in low risk bladder cancer compared to high risk disease. No health economic evidence was identified.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of the recommendation is more accurate diagnosis of upper tract tumours in high risk bladder cancer, which should result in better clinical outcomes. The recommendation should lead to the avoidance of invasive tests in low risk disease. The GDG considered the potential harms of upper tract imaging such as

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	relative radiation and contrast related toxicities. There is the potential harm of missing upper tract tumours in low risk disease. The GDG considered that the excess risk is less than the increased clinical benefit.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The costs of the recommendations will result from the increased relative costs of CTU, which is more expensive than IVU. There may be an increase in the number of CTU performed. The GDG balanced this cost against the potential saving from targeting CTU to high risk groups. It is unclear if the recommendation will result in a net increase or decrease in costs.
Other considerations	No equalities issued were identified for this topic. The GDG were unsure of the extent of change in practice required to implement the recommendation. They considered that the move towards CTU away from IVU is already happening clinically. The GDG extensively discussed making a do not use recommendation for upper tract imaging in patients with low risk NMIBC. There was insufficient high quality evidence to make this recommendation, although the clinical judgment of the GDG is that upper tract imaging in this patient group is of limited benefit. Having reviewed all section 3.4 recommendations, the GDG suggested that CT urogram should be combined with other CT imaging to streamline the diagnostic pathway.

3.4.3 Detecting thoracic malignancy

The main aim of thoracic imaging is to detect metastatic spread from bladder cancer. However, in people with bladder cancer who have smoked, there may be an increased risk of lung cancer which can also be detected by imaging the thorax. Detection of another malignancy would affect treatment planning.

The thorax can be assessed by plain X-ray, CT, MRI or PET-CT. Plain X-ray and CT are used most in the NHS. CT gives much more detail than plain X-ray and shows small abnormalities that plain X-ray cannot but it is much more expensive. PET-CT can be used to assess the thorax but is not widely available because of strict NHS commissioning rules on its use in bladder cancer

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

Clinical evidence (see also full evidence review)

Study quality and results

Two observational studies were included in the evidence review (Lodde *et al.*, 2010; Yang *et al.*, 2012a). Risk of bias and applicability were assessed using the QUADAS-2 tool. Both studies were applicable to the review question. Both studies had a low risk of bias for patient selection, although in Lodde *et al.* (2010) it was unclear if a consecutive or random sample of patients was used. Studies were judged to have a high or unclear risk of index test bias because the index test was reported with knowledge of clinical history or the results of other imaging tests. In both studies it was unclear if the reference standard was interpreted

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without knowledge of the index test. In Yang *et al.* (2012a) not all patients received the same reference standard. Lodde *et al.* (2010) did not report the sensitivity and specificity of CT and PET-CT for detecting thoracic malignancies. For these reasons the results of the studies were not pooled.

Evidence statements

Moderate quality evidence from two studies which investigated whole body FDG PET-CT scans for the staging of bladder cancer was identified. Lodde *et al.* (2010) included 44 patients with MIBC before radical cystectomy, 19 patients under follow-up after cystectomy, and seven after systemic chemotherapy. For the detection of extrapelvic metastases, 36 patients who had six months or more of imaging follow-up were included. In five patients, standard CT detected lung nodules that did not accumulate FDG, and in one retroperitoneal node, also negative at PET. None of these patients had progressed on subsequent follow-up imaging. Yang *et al.* (2012a) included 60 bladder cancer patients undergoing whole body PET-CT for routine follow-up, for the detection of suspected metastasis, or for monitoring treatments. 15 lung lesions were indentified. The sensitivity and specificity of PET-CT for detecting lung metastases was 85.7% and 100%, respectively. Two lung lesions were considered to be false negative, as they were validated to be malignant during follow-up, but with no abnormal FDG uptake. Both lesions were smaller than 1.5cm, so the diagnosis of CT was also ambiguous. PET-CT correctly changed the management in 15 (25%) patients.

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

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider CT of the thorax, carried out with other planned CT imaging if possible, to detect thoracic malignancy in people with muscle-invasive bladder cancer.**
Relative value placed on the outcomes considered	Sensitivity and specificity were considered by the GDG to be the most important outcomes because accurate detection of lung malignancy is an important diagnosis to make and can affect management of the disease. The outcomes of overall survival, progression-free survival, and morbidity associated with the procedure were specified in the PICO but were not reported in the evidence. Change in management was not considered to be a useful outcome as the patient numbers in the included studies were so small.
Quality of the evidence	The evidence was assessed as being of moderate quality using the QUADAS-2 tool. There were many limitations of the evidence, most notably the retrospective design of the studies, the lack of evidence on chest x-ray versus chest CT, and a lack of evidence about non-muscle invasive bladder cancer. The included studies included a small number of patients and included patients at the end of chemotherapy.

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	These limitations affected the strength of the recommendation. A 'consider' rather than an 'offer' recommendation was made. No recommendation could be made for patients with NMIBC. The GDG based the recommendation on clinical consensus that thoracic malignancy would be very low in patients with NMIBC and so they would not recommend imaging in these patients. No health economic evidence was identified.
Trade-off between clinical benefits and harms	The GDG considered a potential benefit of the recommendation to be the detection of thoracic malignancy which will prevent inappropriate cystectomies. There is also a potential clinical benefit from treating primary lung cancer. The GDG considered the potential harms of radiation from imaging and the potential for over-investigation of false positive imaging results. False positives may potentially delay radical treatment. The GDG considered that the excess risk is less than the increased clinical benefit. The GDG's priority is to avoid inappropriate cystectomies or other radical treatment.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The costs of the recommendations will result from the increased number of thoracic CTs performed and the relative increase in cost of doing CT instead of chest x-ray. The GDG considered the potential savings from a possible reduction in PET-CTs through identification of gross pathology on CT and a reduction in inappropriate radical treatment costs. Overall, the GDG expect the net effect to be fairly small.
Other considerations	No equalities issued were identified for this topic. The GDG considered that a small change in practice will be required to implement the recommendation. The recommendation should require the need to include the thorax in CT examinations. The GDG extensively discussed a recommendation about imaging the chest in NMIBC. The GDG also gave consideration to the increased risk of primary lung cancer within this group but this was considered to be outside the scope of this group's remit. Having reviewed all section 3.4 recommendations the GDG suggested that CT thorax should be combined with other CT imaging to streamline the diagnostic pathway.

3.4.4 Detecting bone metastases

Bone metastases are uncommon in bladder cancer but profoundly affect prognosis and therefore treatment options. Bone can be assessed by bone scintigraphy, CT, MRI or PET CT. Imaging to detect bone metastases in people with bladder cancer is not done frequently in the NHS, but where undertaken, bone scintigraphy is usually used. Cross sectional imaging techniques may distinguish between cancer and conditions such as arthritis, whereas bone scintigraphy is less good at this.

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Clinical question: In patients with high risk NMIBC or MIBC is CT, MRI or bone scintigraphy the most effective method for the detection of bone metastases and can these tests be omitted in patients with NMIBC?

Clinical evidence (see also full evidence review)

Study quality and results

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

Evidence statements

Two studies (86 patients in total) provided low quality evidence that the sensitivity and specificity of MRI and PET-CT were higher for the detection of bone metastases than bone scintigraphy (Balliu *et al.*, 2010; Chakraborty *et al.*, 2013). Low quality indirect evidence was identified from five studies which reported the clinical value of bone scans in 623 bladder cancer patients (Braendengen *et al.*, 1996; Brismar & Gustafson, 1988; Davey *et al.*, 1985; Yang *et al.*, 2012b; Lodde *et al.*, 2010). These studies included patients undergoing routine bone scintigraphy for staging bladder cancer or because of a suspicion of bone metastases. The prevalence of bone metastases varied across studies from 6% to 23%. No evidence was identified for patients with non-muscle invasive bladder cancer. No evidence was identified for the outcomes of overall survival, progression-free survival or morbidity associated with procedure.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	No recommendation made
Relative value placed on the outcomes considered	Sensitivity and specificity were considered by the GDG to be the most important outcomes because accurate detection of bone metastases is an important diagnosis to make and can affect management of the disease. The outcomes of change in management, overall survival, progression-free survival, and morbidity associated with the procedure were specified in the PICO but were not reported in the evidence. The outcome of incidence of bone metastases in asymptomatic patients was not specified in the PICO but was reported in the evidence and discussed by the GDG. This is the patient group where the use of the test would change management.

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Quality of the evidence	The evidence was assessed as being of low quality using the QUADAS-2 tool. There were many limitations of the evidence, most notably the lack of relevant comparative studies, with one study including mostly breast and lung cancer patients. There was a low event rate in the relevant studies and some studies dated back to the 1980s.There was a lack of evidence about CT. There were many patients with symptomatic lesions in the study groups. No recommendation was made because there was insufficient high quality evidence on techniques looking primarily at bone metastases, and because the GDG felt that the other recommendations made for CT and MRI would likely pick up those people with bone metastases in any event. No research recommendation was made as the GDG had made a recommendation elsewhere that people with the highest risk of bone metastases would have PET-CT and that for other people with bladder cancer, a study of detection methods for bone metastases was unlikely to change clinical practice and was unlikely to be a good use of research funding.
Trade-off between clinical benefits and harms	
Trade-off between net health benefits and resource use	
Other considerations	There was insufficient evidence on which to make a recommendation. FDG PET CT is considered a good technique for detection of bone metastases and there is no current evidence of superiority for other techniques. However the GDG recognized that data on some of these techniques is immature. FDG PET is the most widely available technique and the GDG considered that people with bone metastases would be picked up by the recommendations made in section 3.4

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4 Managing non-muscle-invasive bladder cancer

Most people with bladder cancer do not have cancer in the muscle wall of the bladder (muscle invasive bladder cancer), but have cancer that involves the surface lining of the bladder (urothelium), or the connective tissue layer (lamina propria) that connects the surface lining to the main muscle coat (non-muscle invasive bladder cancer). These cancers are designated stages pTa and pT1 respectively, and they are also classified according to whether they are regarded as not aggressive, moderately aggressive, or aggressive, grades 1, 2 and 3 respectively.

The majority of people with bladder cancer will have pTa cancers of either grade 1 or 2. These cancers may return on the lining of the bladder (recurrence), or worsen, meaning return and extend to involve the main muscle coat of the bladder or beyond (progression).

Recurrence of non-muscle invasive bladder cancer is generally not life-threatening. However, people with NMIBC will need cystoscopy under anaesthesia to remove the recurrence, with the time in hospital and recovery time, and the possibility of additional treatment and follow up. Recurrence is important to the NHS because of the costs and capacity needed to treat it.

Progression, in contrast, means that the risk to life has risen and that further investigations and more invasive treatment options will be considered. If progression of the cancer to involvement of the muscle wall of the bladder occurs, 20 - 25 out of 100 such people will also have spread into their lymph glands, and their chance of cure falls sharply.

People with non-muscle invasive bladder cancer may have different experiences following their inital transurethral resection. The information people receive about what was seen and done at the operation may vary in quality, quanitity and how it is communicated and this will impact on the patients understanding of their condition and ability to make informed decisions.

There may be some form of imaging, and there will be further cystoscopy follow-up, which may be infrequent for many people. For some people there will be repeat resection and discussion of treatment options that include intravesical therapy (chemotherapy or BCG) and radical cystectomy. The subsequent pathways for people with non muscle invasive bladder cancer may therefore be very different.

The impact of this on the people involved will differ, and their concerns may be very different, but include such questions as:

- Is this cancer life-threatening ?
- Will I lose my bladder ?
- For how long will I need to be treated?
- Is recurrence a sign that the cancer has spread ?
- For how long will I need to be followed-up and will my appointments be forgotten?
- Will I become incontinent ?
- Will my sexual function be lost ?

Some of the important issues in non-muscle invasive bladder cancer are, therefore:

- Prognostic factors
- Staging, including transurethral surgery and imaging
- The risk of recurrence and progression, and its classification
- Adjuvant treatment, including intravesical therapy and radical cystectomy
- Follow-up

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There is uncertainty and variation in practice in all of these areas at present.

4.1 Risk Stratification

4.1.1 Prognostic markers in non-muscle-invasive bladder cancer

Assessment of the risk of recurrence and progression is critical to choosing the optimal package of care. Prognostic markers include clinical factors such as history of recurrence and pathological characteristics including:

- stage
- grade
- cancer size
- the presence of carcinoma *in situ*
- number of cancers
- variant pathology
- lymphovascular invasion.

There is no widely agreed and implemented method of assessing risk of recurrence and progression using prognostic markers.

Clinical question: Which factors determine risk of relapse and progression in newly diagnosed non-muscle invasive bladder cancer (e.g. histological grading of bladder cancer)? In addition to the factors specified in the EORTC risk tables, do urothelial cancer variants, differentiation of urothelial cancer and lymphovascular invasion predict recurrence and progression after treatment?

Clinical evidence (see also full evidence review)

Study quality and results

The NICE prognostic studies methodological checklist was used to assess the quality of the prognostic studies. All studies were assessed as being of high quality as they included the population of interest, measured the outcome adequately, and used appropriate statistical analysis. However, validation studies of the EORTC risk tables were limited by heterogeneous patient populations and treatments received and by low numbers of progression events. Studies exploring the prognostic factors of lymphovascular invasion, urothelial cancer variants and urothelial cancer differentiation were limited by small sample sizes and few patients with the factor under investigation.

Evidence statements

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

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

One study (Brimo *et al.*, 2013) of 86 patients reported that adverse histological variants were significantly associated with progression and recurrence on univariate analysis but were

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insignificant on multivariate analysis. Only four tumours were not 'usual' TCC. Three had features of micropapillary TCC and one had features of sarcomatoid TCC.

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

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

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Record the size and number of tumours during TURBT.** **Ensure that for people with non-muscle-invasive bladder cancer all of the following are recorded and used to guide discussions, both within multidisciplinary team meetings and with the person, about prognosis and treatment options:** • **recurrence history** • **size and number of cancers** • **histological type, grade, stage and presence (or absence) of flat urothelium, detrusor muscle (muscularis propria), and carcinoma in situ** • **the risk category of the person's cancer (see section 4.1.2)** • **predicted risk of recurrence and progression, estimated using a risk prediction tool.**
Relative value placed on the outcomes considered	The GDG considered the cancer-related outcomes of recurrence, disease progression, disease-specific survival and overall survival as important outcomes. Recurrence and progression lead to further treatment and potentially a worse prognosis. Survival is important for patients. Overall survival was specified as an outcome in the PICO but was not reported in the evidence.
Quality of the evidence	The quality of the evidence was assessed as high using the NICE methodology checklist for prognostic studies. However, the reviewer highlighted some issues with the evidence. Most notably, the EORTC risk calculator is limited in that it overestimates recurrence in patients treated with BCG. Validation studies of the EORTC risk tables were limited by heterogeneous patient populations and treatments received and by low numbers of progression events. Studies exploring the prognostic factors of lymphovascular invasion, urothelial cancer variants and urothelial cancer differentiation were limited by small sample sizes, with few patients with the factor under investigation. However the GDG considered that the high quality evidence of the EORTC risk factors and validation studies strengthened the case for making the recommendations.

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Trade-off between clinical benefits and harms	The GDG considered that the main benefits of the recommendations are better informed decision making by the person and the implementation of existing guidelines and improvements in the quality of data collected to guide future clinical management of non-muscle invasive bladder cancer. The GDG identified no potential harms from the recommendations made.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG considered the potential costs and savings associated with the recommendation made. The potential costs include more staff time at MDT meetings to consider the clinical and histological prognostic factors listed in the recommendation. This was balanced against the potential savings accrued from better treatment and less need for subsequent salvage treatment. Savings will also be made from the avoidance of unnecessary treatment and follow-up.
Other considerations	No equalities issues were identified. The GDG considered that a moderate change in practice may be required to implement the recommendations. EORTC and RCPath datasets should be used routinely in local and specialist bladder MDTs, so the recommendations reflect best practice.

4.1.2 Definitions of risk

There is no widely accepted classification of risk in non-muscle invasive bladder cancer. In order to make clear recommendations for management, the GDG developed a consensus classification based on evidence reviewed and clinical opinion. For the purposes of this guideline the following definitions apply:

For this purpose, we refer only to **non-muscle invasive urothelial cancer**, not muscle invasive cancer or non-urothelial cancers.

Low risk NMIBC

Any of these:

- Solitary pTaG1 <3cm
- Solitary pTaG2 (low grade) <3cm
- Any PUNLMP (papillary urothelial neoplasm of low malignant potential)

Intermediate risk NMIBC

Any tumour that is not low risk or high risk including the following:

- Solitary pTaG1 ≥3cm
- Multifocal pTaG1
- Solitary pTaG2 (low grade) ≥3cm
- Multifocal pTaG2 (low grade)
- pTaG2 (high grade)
- Any pTaG2 (grade not further specified)
- Any low risk recurring within 12 months from last tumour occurrence

High risk NMIBC

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Any of these:

- pTaG3
- pT1G2
- pT1G3
- pTis (Cis)
- aggressive variants of urothelial carcinoma, for example micropapillary or nested variants

4.2 Managing non-muscle invasive bladder cancer

4.2.1 Intravesical therapy

Intravesical therapy involves the instillation into the bladder of either a chemotherapy drug (in the NHS this is typically Mytomycin C) or BCG. Intravesical chemotherapy is most often given as a single dose directly following transurethral resection of a cancer to try to prevent recurrence of non-muscle invasive bladder cancer. It can also be used on an outpatient basis as a course of treatment to try to reduce recurrence in people who have had a significant rate of recurrence.

Intravesical BCG is an immunotherapy used to treat intermediate and high-risk non-muscle invasive bladder cancer. Each treatment includes the instillation of live BCG bacteria, of which various strains are known to exist, into the bladder. Intravesical BCG is given on an outpatient basis as a course of treatment, to try to prevent recurrence and also progression in people judged to have a significant risk of these problems. In the most commonly used regimen it is given as a course of six instillations (induction BCG) followed by sets of 3 instillations over a period of up to 3 years (maintenance BCG).

Some people relapse after BCG, their management is discussed in section 4.3.2. The management of BCG-related toxicity is discussed in section 4.4.

There is wide variation in practice regarding the use of intravesical chemotherapy and intravesical BCG in the NHS at present.

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

Clinical evidence (see also full evidence review)

Systematic reviews and randomised trial evidence was appraised for this review. The evidence is summarised in tables 28 to 54.

Evidence statements

TUR + BCG versus TUR alone

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

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

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

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

TUR + chemotherapy versus TUR alone

One systematic review and meta-analysis of 11 studies and 3,703 patients with primary bladder cancer provides a Peto Odds Ratio (pOR) of 0.56 (95% CI 0.48 to 0.65) for one-year recurrence in favour of adjuvant intravesical chemotherapy compared to TUR alone (Huncharek et al., 2000). However, significant statistical heterogeneity is reported and sensitivity analyses were conducted. The data were stratified by duration of treatment, which indicates that short-term therapy (≤2 months duration) reduces recurrence at one-year (pOR 0.70, 95% CI 0.55 to 0.90) and two-years (pOR 0.68, 95% CI 0.54 to 0.85) by approximately 30%, as compared to TUR alone (moderate quality evidence). The pOR for five trials where patients received two years of chemotherapy is 0.27 (95% CI 0.19 to 0.39), indicating a 73% reduction in the risk of recurrence at two-years for those treated with chemotherapy.

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

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

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

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

TUR+ single dose epirubicin versus TUR + double dose Epirubicin

Low quality evidence from one randomised trial of 143 patients without CIS suggests no difference in recurrence or progression between patients treated with a single dose of 100mg epirubicin within six hours of TUR and those given a second dose of 100mg epirubicin 12-18 hours after TUR (Turkeri et al., 2010).

Moderate quality evidence from one trial of 270 patients without CIS reports that two instillations of 50mg epirubicin within 24 hours of TUR is associated with longer recurrence-free survival than TUR alone (38 months versus 13 months, p=0.004). Recurrence-free survival with two instillations of lower dose epirubicin (20mg/40ml) is not significantly longer than TUR alone (24 months versus 13 months, p=0.163). There are no significant differences between 2x50mg and 2x20mg epirubicin (p=0.146). Local grade one toxicity was reported in 22.9% of the low dose epirubicin group and 35.6% of high dose epirubicin group (RR 0.63, 95% CI 0.39 to 1.02).

Intravesical Adriamycin versus Epirubicin

Moderate quality evidence is provided by two randomised trials comparing one year treatment with adriamycin with the same schedule of epirubicin (Eto et al., 1994; Shuin et al., 1994). There were no differences in recurrence rate (RR 1.31, 95% CI 0.72 to 2.4) or local toxicities (RR 0.73, 95% CI 0.46 to 1.15) between the two treatment arms.

Adjuvant intravesical BCG versus adjuvant intravesical chemotherapy

One systematic review of nine trials and 2,261 patients (Huncharek & Kupelnick 2003) reports low quality evidence of an overall OR for one-year recurrence of 0.89 (95% CI 0.74 to 1.07), with significant heterogeneity. Heterogeneity persisted despite stratification by chemotherapy drug type. A sensitivity analysis was therefore performed stratifying by previous intravesical chemotherapy. Pooling all studies that enrolled patients with prior chemotherapy (1480 patients) provides moderate quality evidence, with an OR of 0.54 (95% CI 0.43 to 0.69) in favour of BCG. This reflects a 46% reduction in tumour recurrence at one-year among patients treated with BCG versus chemotherapy, and a lack of statistical heterogeneity. Pooling data from two studies which excluded patients previously treated with chemotherapy gives an OR of 1.82 (95% CI 1.37 to 2.41), in favour of chemotherapy. This suggests that amongst patients not previously treated, intravesical chemotherapy (MMC) reduces tumour recurrence by 82% versus BCG. Similar results were found for two-year and three-year recurrence when stratified by previous therapy.

One systematic review of eight randomised trials and 2,427 patients (Huncharek & Kupelnick 2004) randomised to either adjuvant intravesical BCG or chemotherapy provides moderate quality evidence of an OR for progression of 1.24 (95% CI 0.95 to 1.61), in favour of BCG. The confidence intervals include the value of no effect which reflects uncertainty about a

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difference in progression between the two treatments. The total number of events in each arm is not reported. The pooled OR of the two trials (781 patients) which excluded patients who had previously been treated with intravesical chemotherapy is 0.75 (0.45 to 1.25) in favour of MMC. In trials which included patients previously treated with chemotherapy the OR is 1.49 (1.09 to 2.03) in favour of BCG.

One meta-analysis (Sylvester et al., 2005) of nine randomised trials and 700 patients with CIS provides moderate quality evidence that 34% of complete responders treated with BCG and 50% of complete responders treated with chemotherapy recurred during follow-up (HR 0.47, 95% CI 0.31 to 0.73, in favour of BCG). 47% of patients treated with BCG and 26% treated with chemotherapy had no evidence of disease during follow-up, relating to an absolute difference of 20% and a relative reduction of 59% in the odds of treatment failure on BCG (HR 0.41, 95% CI 0.30 to 0.56). BCG is only superior to MMC in the trials where maintenance BCG was given. Data on progression were less conclusive with a HR of 0.74 (95% CI 0.45 to 1.22). Overall survival is reported in three studies (407 patients). 35.9% of patients treated with chemotherapy and 34.2% treated with BCG therapy died from any cause. Two trials reported disease-specific survival. 13.3% of patients treated with chemotherapy and 10.5% of patients treated with BCG died due to bladder cancer.

BCG versus Mitomycin C (MMC)

Moderate quality evidence is reported from one meta-analysis (Bohle et al., 2003) of 2,749 patients from nine prospective trials and two observational studies. A further trial of 92 patients was indentified and added to the pooled analysis for recurrence (Mangiarotti et al., 2008). The overall RR for recurrence is 0.77 (95% CI 0.63 to 0.95) in favour of BCG over MMC. High quality evidence from a meta-analysis of individual patient data (Malmstrom et al., 2009) including nine trials (2,820 patients) reported that in trials with BCG maintenance, there is a 32% reduction in the risk of recurrence with BCG compared to MMC (HR 0.68, 95% CI 0.58 to 8), whilst there is a 28% risk increase for BCG trials without maintenance (HR 1.28, 95% CI 1.07 to 1.52). Maintenance BCG is more effective than MMC in both patients previously treated and those not previously treated with intravesical chemotherapy.

Moderate quality evidence from one meta-analysis including 1,277 patients (Bohle & Bock 2004) reports no difference between BCG and MMC in terms of disease progression (RR 0.79, 95% CI 0.61 to 1.03). However, BCG does show superiority over MMC in the subgroup of BCG maintenance trials (RR 0.70, 95% CI 0.52 to 0.94). Moderate quality evidence from seven trials (1,880 patients) in the IPD meta-analyses reports that after a median follow-up of 4.8 years, 12% of patients progressed and 24% died (of those 30% died from bladder cancer). There are no significant differences between MMC and BCG for these end-points, even when stratified by BCG maintenance and patient risk groups.

Cystitis was more frequent in the BCG group compared to the MMC group (53.8% vs. 39.2%, $p<0.001$). Local and systemic toxicities were more frequent in the BCG group, except for allergy and skin reactions which were more common in MMC group. The risk of cystitis was no different between maintenance BCG and no maintenance BCG. No deaths from sepsis were reported in either arm (Bohle et al., 2003).

BCG versus Epirubicin (EPI)

Moderate quality evidence from one meta-analysis of five randomised trials (1,111 patients) (Shang et al., 2011), reports that the risk of recurrence was reduced in patients treated with BCG (35.9%) compared to EPI (51.4%) with a RR of 0.69 (95% CI 0.60 to 0.79), in favour of BCG. Low quality evidence from a subgroup analysis demonstrates no significant difference in recurrence between BCG and EPI in two trials using Pasteur strain BCG (RR 0.78, 95% CI 0.56 to 1.10). Low quality evidence for disease progression demonstrated that there are no significant differences between BCG and EPI (RR 0.78, 95% CI 0.54 to 1.13). No differences are reported for overall mortality (two studies, 769 patients) or disease-specific mortality (two studies, 769 patients). However, overall mortality is less frequent in the TICE

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BCG group compared to the EPI group in the study by Sylvester et al. (2010) (RR 0.79, 95% CI 0.62 to 0.99). Drug-induced cystitis (54% versus 32%), haematuria (31% versus 16%), and systemic side-effects (35% versus 1%) are significantly more frequent with BCG than EPI. However, there is significant heterogeneity between trials for systemic side-effects due to the frequency of BCG administration across studies. Moderate quality evidence from four randomised trials suggests there are no significant differences for delayed or terminated treatment due to adverse events between BCG and EPI (9% versus 7%) (RR 0.91, 95% CI 0.41 to 2.04).

BCG versus Gemcitabine

One systematic review by Jones et al. (2012) includes three studies comparing Gemcitabine with BCG. Heterogeneity between trials prevented pooling of data. One trial of 80 patients at intermediate risk of recurrence (primary Ta-T1, no CIS) provides low quality evidence that BCG (no maintenance) and Gemcitabine showed similar rates of recurrence (25% vs. 30%) and progression, with significantly more adverse effects with BCG. Moderate quality evidence is provided by one trial of 64 high risk patients, which reports that recurrence rate is higher for Gemcitabine than BCG (53% vs. 28%) and time to recurrence is shorter with Gemcitabine (25.6 months vs. 39.4 months). No patients in either group had disease progression at a mean follow-up of 44 months. Local and systemic toxicity are similar between groups. In this trial, maintenance therapy for non-recurring patients in each group was up to 36 months duration. No evidence about survival is reported.

Maintenance BCG versus induction BCG

Six trials of maintenance versus induction BCG were indentified which vary in the population included and the schedule and duration of maintenance therapy. High quality evidence from five of these trials with 686 patients, reports that 53.9% of patients in the BCG induction arm had a recurrence, compared to 37.6% in the maintenance BCG arm (RR 0.70, 95% CI 0.60 to 0.81). Moderate quality evidence from five trials (737 patients) suggests similar rates of progression (27.6% versus 31.8% for maintenance and induction BCG respectively). However, these data should be interpreted with caution due to the variation in BCG maintenance schedules and the duration of follow-up across studies. There are no differences between groups in terms of overall survival and disease-specific survival. Moderate quality evidence from two trials (126 patients) suggests that dysuria is more frequent in the maintenance arm (88.9% versus 68.3%). Rates of fever/chills are not different between groups (RR 1.47, 95% CI 0.88 to 2.44).

One trial of 53 patients reported moderate quality evidence of no significant changes in quality of life scores (EORTC-QLQ) in either group from induction treatment to 14 months after randomisation (Koga et al., 2010). Very low quality evidence from one observational study of 85 patients reports that overall quality of life was moderate, and more patients rated it as good during maintenance than during induction therapy (Mack et al., 1996).

Dose of BCG

Low dose versus standard dose BCG

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

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One trial of 80 patients provides low quality evidence of no difference in recurrence, progression or cystitis between patients receiving 81mg BCG versus those receiving 54mg BCG (Yalcinkaya et al., 1998). One trial of 128 patients randomised into three arms, provides low quality evidence of no difference in recurrence rates between 120mg BCG, 80mg BCG and 40mg BCG. No patients had disease progression. Both local toxicity and systemic toxicity were reduced with lower dose of BCG (Agrawal et al., 2007).

Low dose versus very low dose BCG

Moderate quality evidence from one trial of 281 patients (Ojea et al., 2007) suggests that there are no differences in recurrence-free survival between low dose BCG (27mg) and very-low dose BCG (13.5mg) in intermediate risk patients. There are no differences in time to progression and cancer-specific survival between the two BCG treatment groups. Rates of local (65.5% vs. 64.1%) and systemic (11.3% vs. 10.8%) adverse events are also similar between the two groups.

Low dose and standard dose with 1 year or 3 year maintenance

Moderate quality evidence is provided by one trial of 1,355 patients randomised into four trial arms (Oddens et al., 2013). With a median follow-up of 7.1 years, no differences are reported for recurrence, progression, overall survival and toxicity between one-third (27mg) dose and full dose (81mg) BCG. When results are stratified by maintenance and dose, one-third dose BCG with one-year maintenance is suboptimal compared to full-dose BCG with three-year maintenance (HR for disease-free interval 0.75, 95% CI 0.59 to 0.94). In intermediate-risk patients, three years of maintenance is more effective than one year in patients receiving one-third dose (HR 1.35, 95% CI 1.03 to 1.79) but not in patients receiving full-dose (HR 0.88, 95% CI 0.64 to 1.21). In high-risk patients, three years of maintenance is more effective than one year in patients receiving full dose (HR 1.61, 95% CI 1.13 to 2.30) but not in patients receiving one-third dose BCG (HR 1.01, 95% CI 0.69 to 1.47). No significant differences are reported between treatment groups for the time to progression or overall survival.

The schedule and duration of intravesical chemotherapy

One systematic review of 23 randomised trials (Sylvester et al., 2008) which compared intravesical instillations with respect to their number, frequency, timing, duration, dose, or dose intensity concludes that the optimal schedule and duration of intravesical chemotherapy after an immediate instillation remains unknown. In low-risk patients, one immediate instillation of epirubicin may not be less effective than a delayed course of multiple instillations (3 trials, 879 patients). In patients with multiple tumours, one immediate instillation is insufficient treatment. Additional instillations may further reduce the recurrence rate; however, there is no conclusive evidence regarding their optimal duration (3 trials, 598 patients). A short intensive schedule of instillations within the first 3–4 months after an immediate instillation may be as effective as longer-term treatment schedules. Instillations during ≥1 year in intermediate-risk patients seem effective only when an immediate instillation has not been given. Higher drug concentrations and optimization of the drug's concentration in the bladder may provide better results (5 trials, 774 patients).

Chemotherapy + maintenance BCG versus maintenance BCG alone

Low quality evidence is provided by a systematic review of four randomised trials (801 patients) comparing sequential chemotherapy added to maintenance BCG with maintenance BCG alone (Houghton et al., 2012). A further study of 96 patients with CIS which compared MMC and BCG with BCG alone was also identified and added to the meta-analysis (Oosterlinck et al., 2011). The dose and duration of intravesical therapies used and the average length of follow-up varies across trials. Meta-analysis of five trials provides low quality evidence of uncertainty of a difference in recurrence between the combination arms (42.6%) and the BCG-alone arms (46.7%) (RR 0.92, 95% CI 0.79 to 1.08), but significant

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heterogeneity (p=0.03). Sub-group analyses provides moderate quality evidence that adding chemotherapy to maintenance BCG was associated with lower recurrence than BCG alone for Ta or T1 disease (RR 0.75, 95% CI 0.61 to 0.92), but not for CIS (RR 1.13, 95% CI 0.93 to 1.37).

Meta-analysis of five trials (897 patients) provides low quality evidence of no significant difference in progression between the combination arms (11.1%) and the BCG-alone arms (13%) (RR 0.84, 95% CI 0.59 to 1.20), but significant heterogeneity (p=0.03). Sub-group analyses provide moderate quality evidence that adding chemotherapy to maintenance BCG is associated with lower progression than BCG alone for Ta or T1 disease (RR 0.45, 95% CI 0.25 to 0.81), but not for CIS (RR 1.33, 95% CI 0.83 to 2.13). Three studies report drug-related toxicity, with no differences in cystitis, haematuria or fever between groups. The numbers of adverse events in each arm is not reported.

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Table 28: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: TUR + BCG versus TUR alone

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR + BCG	TUR alone	Relative (95% CI)	Absolute	Quality
Recurrence at 12 months											
6[1]	randomised trials	none	none	none	serious[2]	none	79/275 (28.7%)	144/257 (56%)	RR 0.54 (0.44 to 0.66)	258 fewer per 1000 (from 191 fewer to 314 fewer)	MODERATE
Recurrence at 12 months - Medium/high risk patients											
4[1]	randomised trials	none	none	none	serious[2]	none	64/188 (34%)	117/204 (57.4%)	RR 0.59 (0.47 to 0.73)	235 fewer per 1000 (from 155 fewer to 304 fewer)	MODERATE
Recurrence at 12 months - Medium/high risk but possibly some low risk											
2[1]	randomised trials	none	none	none	serious[2]	none	15/87 (17.2%)	27/53 (50.9%)	RR 0.35 (0.21 to 0.61)	331 fewer per 1000 (from 199 fewer to 402 fewer)	MODERATE
Recurrence (time-to-event data, follow-up 14 to 36 months)											
6[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	HR 0.44 (0.34 to 0.56)	56% reduction in the risk of recurrence in favour of BCG	MODERATE
Recurrence - Medium/high risk patients (time-to-event data, follow-up 14 to 36 months)											
4[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	HR 0.46 (0.34 to 0.61)	54% reduction in the risk of recurrence in favour of BCG	MODERATE
Recurrence - Medium/high risk but possibly some low risk (time-to-event data, follow-up 14 to 36 months)											
2[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	HR 0.37 (0.22 to (0.64)	63% reduction in the risk of recurrence in favour of BCG	MODERATE
Progression											
0	No evidence										
Overall survival											
0	No evidence										
Disease-specific survival											
0	No evidence										
Treatment-related morbidity											
6[1]	randomised trials	none	none	none	serious[2]	none	-[4]	NR	-	Main toxicities associated with BCG: 67% cystitis, 23% haematuria, 25% fever, 71%	MODERATE

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Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TUR + BCG**	**TUR alone**	**Relative (95% CI)**	**Absolute**	
										urinary frequency	
Treatment-related mortality (follow-up 14 to 36 months)											
6[1]	randomised trials	none	none	none	serious[2]	none	0/275 (0%)	0/257 (0%)	-	-	MODERATE
Health-related quality of life											
0	No evidence										

[1] From meta-analysis in Shelley et al. (2000); 2 Low number of events reduces precision; 3 Number of events not reported in Shelley et al. 2000; 4 Main toxicities associated with BCG: 67% cystitis, 23% haematuria, 25% fever, 71% urinary frequency. No BCG sepsis or deaths reported

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Table 29: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: TUR + BCG versus TUR + other treatment (chemotherapy or other immunotherapy) or TUR alone

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR+BCG	TUR+other treatment	Relative (95% CI)	Absolute	Quality
Recurrence											
48[1]	randomised trials & observational studies	none	serious[2]	none	none	none	1900/4952 (38.4%)	2231/4530 (49.2%)	OR 0.59 (0.49 to 0.71)[3]	128 fewer per 1000 (from 85 fewer to 170 fewer)	MODERATE
Recurrence by BCG maintenance											
8[4]	randomised trials & observational studies	none	None	none	none	none	224/596 (37.6%)	243/474 (51.3%)	RR 0.65 (0.48 to 0.88)[3]	179 fewer per 1000 (from 62 fewer to 267 fewer)	HIGH
Recurrence by induction BCG only											
10[4]	randomised trials & observational studies	none	serious[2]	none	serious[5]	none	458/963 (47.6%)	570/1109 (51.4%)	RR 0.99 (0.77 to 1.28)[3]	5 fewer per 1000 (from 118 fewer to 144 more)	LOW
Recurrence, BCG+TUR vs TUR alone											
9[4]	randomised trials & observational studies	none	None	none	None	none	230/638 (36.1%)	268/462 (58%)	RR 0.59 (0.45 to 0.78)[3]	238 fewer per 1000 (from 128 fewer to 319 fewer)	HIGH
Recurrence, BCG vs. Chemotherapy											
10[4]	randomised trials & observational studies	none	serious[2]	none	serious[5]	none	378/910 (41.5%)	398/883 (45.1%)	RR 0.94 (0.77 to 1.14)[3]	27 fewer per 1000 (from 104 fewer to 63 more)	LOW
Recurrence, in patients with papillary tumours											
10[4]	randomised trials & observational studies	none	serious[2]	none	None	none	274/653 (42%)	407/718 (56.7%)	RR 0.73 (0.61 to 0.87)[3]	153 fewer per 1000 (from 74 fewer to 221 fewer)	MODERATE
Progression (follow-up median 2.5 years)											
24[6]	randomised trials	none	None	none	None	none	260/2658 (9.8%)	304/2205 (13.8%)	HR 0.73 (0.6 to 0.88)	35 fewer per 1000 (from 15 fewer to 53 fewer)	HIGH
Progression in studies of BCG versus MMC											
6[6]	randomised trials	none	None	none	serious[5]	none	79/1074 (7.4%)	76/816 (9.3%)	HR 0.86 (0.62 to	12 fewer per 1000 (from 34	MODERATE

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Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TUR+BCG**	**TUR+other treatment**	**Relative (95% CI)**	**Absolute**	
									1.2)	fewer to 18 more)	
Overall survival, death due to any cause											
9[6]	randomised trials	none	None	none	serious[5]	none	372/1603 (23.2%)	354/1327 (26.7%)	HR 0.89 (0.75 to 1.06)	25 fewer per 1000 (from 59 fewer to 14 more)	MODERATE
Disease-specific survival, death due to bladder cancer											
8[6]	randomised trials	none	None	none	serious[5]	none	74/1327 (5.6%)	80/1043 (7.7%)	HR 0.81 (0.57 to 1.13)	14 fewer per 1000 (from 32 fewer to 10 more)	MODERATE
Treatment-related morbidity - Local toxicity											
25[4]	randomised trials & observational studies	none	None	none	Serious[7]	none	44%	30% (MMC)[8]	-	-	MODERATE
Treatment-related mortality											
0	No evidence										
Health-related quality of life											
0	No evidence										

[1] From meta-analysis in Pan et al. (2014) –included observational studies in meta-analysis; [2] Significant statistical heterogeneity across studies; [3] Random effects model; [4] From meta-analysis (Han & Pan, 2006); [5] Confidence interval includes null value which limits precision of outcome; [6] From meta-analysis in Sylvester et al. (2002); [7] Number of events not reported for treatment-related morbidity [8] BCG-induced local and systemic effects were significantly more frequent in the BCG group than in the chemotherapy/immunotherapy groups (Han & Pan 2006; Pan et al. 2008). Overall 44% receiving BCG developed local toxicity compared with 30% receiving MMC (Han & Pan, 2006).

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Table 30: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: TUR + BCG versus TUR + other treatment (chemotherapy or other immunotherapy) of TUR alone for T1G3 bladder cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	No BCG	Relative (95% CI)	Absolute	Quality
Recurrence											
15[1]	randomised trials	none	serious[2]	none	none	none	375/915 (41%)	332/733 (45.3%)	RR 0.73 (0.61 to 0.88)	122 fewer per 1000 (from 54 fewer to 177 fewer)	MODERATE

[1] *From meta-analysis in Pan et al. (2008) 2 significant statistical heterogeneity across studies*

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Table 31: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: TUR + chemotherapy versus TUR alone

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR+chemo	TUR alone	Relative (95% CI)	Absolute	Quality
Recurrence - primary cancer (follow-up > 1 year; assessed with: 1-year recurrence rate)											
11[1]	randomised trials	none	serious[2]	none	serious[3]	none	NR	NR	OR 0.56 (0.48 to 0.65)	In favour of intravesical chemotherapy	LOW
Recurrence - short-term treatment (assessed with: 1-year recurrence rate)											
2[1]	randomised trials	none	None	none	serious[3]	none	NR	NR	OR 0.70 (0.55 to 0.90)	In favour of intravesical chemotherapy	MODERATE
Recurrence - short-term treatment (assessed with: 2-year recurrence rate)											
2[1]	randomised trials	none	None	none	serious[3]	none	NR	NR	OR 0.68 (0.54 to 0.85)	In favour of intravesical chemotherapy	MODERATE
Recurrence - long-term treatment (1 year) (assessed with: 1-year recurrence rate)											
3[1]	randomised trials	none	None	none	serious[3]	none	NR	NR	OR 0.65 (0.46 to 0.80)	In favour of intravesical chemotherapy	MODERATE
Recurrence - long-term treatment (1 year) (assessed with: 2-year recurrence rate)											
3[1]	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.69 (0.57 to 0.83)	In favour of intravesical chemotherapy	MODERATE
Recurrence - long-term treatment (2 years) (assessed with: 2 year recurrence rate)											
5[1]	randomised trials	none	None	none	serious[3]	none	NR	NR	OR 0.27 (0.19 to 0.39)	In favour of intravesical chemotherapy	MODERATE
Recurrence - recurrent cancer (assessed with: 1-year recurrence rate)											
8[4]	randomised trials	none	None	none	serious[3]	none	NR	NR	OR 0.62 (0.51 to 0.76)	In favour of intravesical chemotherapy	MODERATE
Recurrence - recurrent cancer (assessed with: 2-year recurrence)											
8[4]	randomised trials	none	serious[2]	none	serious[3]	none	NR	NR	OR 0.46 (0.33 to 0.63)	In favour of intravesical chemotherapy	LOW
Recurrence - adriamycin only (assessed with: 2 year recurrence rate)											
5[4]	randomised trials	none	None	none	serious[3]	none	NR	NR	OR 0.57 (0.43 to 0.75)	In favour of intravesical chemotherapy	MODERATE

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TUR+chemo**	**TUR alone**	**Relative (95% CI)**	**Absolute**	**Quality**
Recurrence - drugs other than adriamycin (assessed with: 2 year recurrence rate)											
6[4]	randomised trials	none	None	none	serious[3]	none	NR	NR	OR 0.27 (0.19 to 0.37)	In favour of intravesical chemotherapy	MODERATE
Progression (follow-up median 5.5 years)											
6[5]	randomised trials	none	None	none	serious[6]	none	189/1629 (11.6%)	80/906 (8.8%)	HR 1.19 (0.97 to 1.47)	16 more per 1000 (from 3 fewer to 39 more)	MODERATE
Overall mortality rate (follow-up median 7.8 years)											
6[5]	randomised trials	none	None	none	serious[6]	none	628/1629 (38.6%)	281/906 (31%)	HR 1.1 (0.95 to 1.27)	25 more per 1000 (from 13 fewer to 66 more)	MODERATE
Disease-specific mortality rate (follow-up median 7.8 years)											
6[5]	randomised trials	none	None	none	serious[6]	none	229/1629 (14.1%)	93/906 (10.3%)	HR 1.1 (NR)	In favour of TUR alone (non-significant)	MODERATE
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From meta-analysis in Huncharek et al. (2000) 2 Significant statistical heterogeneity 3 Number of events/participants in each arm not reported (Huncharek et al., 2000 and 2001) 4 From meta-analysis in Huncharek et al. (2001) 5 From meta-analysis in Pawinski et al. (1996) 6 Low number of events / 95% confidence intervals include null value

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Table 32: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: TUR+ one single post-operative chemotherapy instillation versus TUR alone

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TUR + single dose chemo	TUR alone	Relative (95% CI)	Absolute	Quality
Recurrence - all studies											
18[1]	randomised trials	none	serious[2]	none	none	reporting bias[3]	577/1576 (36.6%)	769/1527 (50.4%)	RR 0.67 (0.56 to 0.79)	166 fewer per 1000 (from 106 fewer to 222 fewer)	LOW
Recurrence – Doxorubicin											
1	randomised trials	none	None	none	serious[4]	none	NR/31	NR/28	RR 0.43 (0.23 to 0.78)	In favour of intravesical chemotherapy	MODERATE
Recurrence – Epirubicin											
6	randomised trials	none	None	none	serious[4]	none	NR/665	NR/685	RR 0.73 (0.66 to 0.82)	In favour of intravesical chemotherapy	MODERATE
Recurrence – Gemcitabine											
1	randomised trials	none	None	none	serious[5]	none	NR/124	NR/124	RR 0.90 (0.57 to 1.42)	In favour of intravesical chemotherapy (non-significant)	MODERATE
Recurrence - Interferon alpha 2b											
1	randomised trials	none	None	none	serious[5]	none	NR/66	NR/66	RR 1.05 (0.80 to 1.38)	In favour of intravesical chemotherapy (non-significant)	MODERATE
Recurrence - Mitomycin C											
6	randomised trials	none	None	none	serious[5]	none	NR/412	NR/432	RR 0.66 (0.56 to 0.78)	In favour of intravesical chemotherapy	MODERATE
Recurrence – Thiotepa											
4	randomised trials	none	None	none	serious[4]	none	NR/197	NR/207	RR 0.76 (0.62 to 0.93)	In favour of intravesical chemotherapy	MODERATE
Recurrence – Pirarubicin											
1	randomised trials	none	None	none	serious[4]	none	NR/81	NR/79	RR 0.40 (0.23 to 0.69)	In favour of intravesical chemotherapy	MODERATE
Progression											
0	No evidence available										

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TUR + single dose chemo**	**TUR alone**	**Relative (95% CI)**	**Absolute**	**Quality**
Disease-specific survival											
0	No evidence available										
Overall survival											
0	No evidence available										
Treatment-related morbidity											
1[b]	randomised trials	serious[f]	None	none	None	none	10% mild bladder symptoms	NR	-	-	MODERATE
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From meta-analysis in Abern et al. (2013) [2] Significant statistical heterogeneity [3] Funnel plots suggested existence of publication bias, suggesting that small trials in the analysis disproportionately contribute to the protective effect of intravesical chemotherapy. [4] Small sample size/ low number of events limits precision. Number of events not reported for the analysis stratified by chemotherapy. [5] Low number of events / confidence intervals include null value [6] From meta-analysis of 7 trials by Sylvester et al. (2004) [7] Number of studies reporting toxicity and number of events for symptoms not reported. Adverse effects of TUR alone not reported. Mild, transient, irritating bladder symptoms including dysuria, frequency and macroscopic haematuria, in approximately 10% of patients.

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Table 33: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: TUR + single dose epirubicin (100mg) versus TUR + double dose epirubicin (2x100mg)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single-dose EPI (100mg)	Double-dose EPI (200mg)	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up 16.9 months)											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	10/68 (14.7%)	16/75 (21.3%)	RR 0.69 (0.34 to 1.41)	66 fewer per 1000 (from 141 fewer to 87 more)	LOW
Progression (follow-up 16.9 months)											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	2/68 (2.9%)	6/75 (8%)	RR 0.37 (0.08 to 1.76)	50 fewer per 1000 (from 74 fewer to 61 more)	LOW
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Turkeri et al. 2010 [2] Method of randomisation, allocation concealment and blinding not reported. Power analyses not reported. No information provided about excluded patients with insufficient follow-up. [3] Low number of events / confidence interval includes null value

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Table 34: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: TUR + 2x20mg/40ml epirubicin versus TUR + 2x50mg/100ml epirubicin versus TUR only

Quality assessment							No of patients			Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A 2x20mg EPI	B 2x50mg EPI	C TUR only	Relative (95% CI)	Absolute	Quality
Recurrence (time-to-event data, follow-up median 44 months)												
1[1]	randomised trials	none	none	none	serious[2]	none	24 mo (n=89)	38 mo (n=90)	13 mo (n=91)	A v B, p=0.194 A v C, p=0.245 B v C, p=0.01	In favour of 2x50mg epirubicin over TUR alone	MODERATE
Progression												
0	No evidence available											
Overall survival												
0	No evidence available											
Disease-specific survival												
0	No evidence available											
Treatment-related mortality												
0	No evidence available											
Local toxicity - Grade 1												
1[1]	randomised trials	none	none	none	serious[3]	none	20/89 (22.5%)	32/90 (35.6%)	NR	RR 0.63 (0.39 to 1.02)	132 fewer per 1000 (from 217 fewer to 7 more)	MODERATE
Systemic adverse events												
1[1]	randomised trials	none	none	none	serious[3]	none	4/89 (4.5%)	6/90 (6.7%)	NR	RR 0.67 (0.2 to 2.31)	22 fewer per 1000 (from 53 fewer to 87 more)	MODERATE
Health-related quality of life												
0	No evidence available											

[1] Saika et al. 2010 [2] Number of events in each arm not reported [3] Low number of events / confidence interval includes null value

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Table 35: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: Adriamycin versus Epirubicin

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADR	EPI	Relative (95% CI)	Absolute	Quality
Recurrence											
2[1]	randomised trials	none	none	none	serious[2]	none	19/87 (21.8%)	15/92 (16.3%)	RR 1.31 (0.72 to 2.4)	51 more per 1000 (from 46 fewer to 228 more)	MODERATE
Local side effects											
2[1]	randomised trials	none	none	none	serious[2]	none	22/87 (25.3%)	32/92 (34.8%)	RR 0.73 (0.46 to 1.15)	94 fewer per 1000 (from 188 fewer to 52 more)	MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] *Eto et al. 1994; Shuin et al. 1994 2 Low number of events / confidence interval includes null value*

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Table 36: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: TUR + chemotherapy versus TUR + BCG

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	Chemotherapy	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up 28-86 months; assessed with: 1-year recurrence)											
9[1]	randomised trials	none	serious[2]	none	serious[3]	none	NR	NR	OR 0.89 (0.74 to 1.07)	In favour of BCG (non-significant)	LOW
Recurrence - prior chemotherapy (assessed with: 1-year recurrence)											
7	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.54 (0.43 to 0.69)	In favour of BCG	MODERATE
Recurrence - no prior chemotherapy (assessed with: 1-year recurrence)											
2	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 1.82 (1.37 to 2.41)	In favour of chemotherapy	MODERATE
Recurrence - prior chemotherapy (assessed with: 3-year recurrence)											
7	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 0.43 (0.34 to 0.55)	In favour of BCG	MODERATE
Recurrence - no prior chemotherapy (assessed with: 2-year recurrence)											
2	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 1.67 (1.29 to 2.17)	In favour of chemotherapy	MODERATE
Progression											
8[4]	randomised trials	none	none	none	serious[5]	none	NR	NR	OR 1.24 (0.95 to 1.61)	In favour of chemotherapy (non-significant)	MODERATE
Progression - prior chemotherapy											
6	randomised trials	none	none	none	serious[3]	none	NR	NR	OR 1.49 (1.09 to 2.03)	In favour of chemotherapy	MODERATE
Progression - no prior chemotherapy											
2	randomised trials	none	none	none	serious[5]	none	NR	NR	OR 0.75 (0.45 to 1.25)	In favour of BCG (non-significant)	MODERATE
Overall survival											
0	No evidence available										
Disease-specific survival											

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Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BCG**	**Chemotherapy**	**Relative (95% CI)**	**Absolute**	
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From meta-analysis in Huncharek & Kupelnick 2003; [2] Significant statistical heterogeneity; [3] Number of patients/events in each arm not reported in Huncharek 2003 and 2004; From meta-analyses in Huncharek & Kupelnick 2004; 5 Number of patients and events not reported. Confidence interval includes null value

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Table 37: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: TUR + chemotherapy versus TUR + BCG for CIS only

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	Chemotherapy	Relative (95% CI)	Absolute	Quality
Recurrence in complete responders (follow-up median 3.6 years)											
7[1]	randomised trials	none	none	none	serious[2]	none	69/203 (34%)	79/158 (50%)	HR 0.48 (0.31 to 0.74)	217 fewer per 1000 (from 99 fewer to 307 fewer)	MODERATE
No evidence of disease (follow-up median 3.6 years)											
9	randomised trials	none	none	none	serious[2]	none	161/345 (46.7%)	93/355 (26.2%)	HR 0.41 (0.3 to 0.56)	145 fewer per 1000 (from 106 fewer to 175 fewer)	MODERATE
Disease-free in studies with MMC according to BCG maintenance (follow-up median 3.6 years)											
5	randomised trials	none	none	none	serious[2,3]	none	78/170 (45.9%)	63/177 (35.6%)	HR 0.7 (0.44 to 1.09)	91 fewer per 1000 (from 180 fewer to 25 more)	MODERATE
Disease-free in studies with MMC according to BCG maintenance - No BCG maintenance											
2	randomised trials	none	none	none	serious[2,3]	none	29/62 (46.8%)	14/28 (50%)	HR 1.24 (0.5 to 3.06)	77 more per 1000 (from 207 fewer to 380 more)	MODERATE
Disease-free in studies with MMC according to BCG maintenance - BCG maintenance											
3	randomised trials	none	none	none	serious[2]	none	49/108 (45.4%)	49/149 (32.9%)	HR 0.58 (0.34 to 0.97)	122 fewer per 1000 (from 8 fewer to 202 fewer)	MODERATE
Progression											
6	randomised trials	none	none	none	serious[2,3]	none	47/240 (19.6%)	36/234 (15.4%)	HR 0.74 (0.45 to 1.21)	35 fewer per 1000 (from 78 fewer to 26 more)	MODERATE
Overall mortality rate (follow-up median 3.6 years)											
3	randomised trials	none	none	none	serious[2]	none	63/184 (34.2%)	80/223 (35.9%)	NR	-	MODERATE
Disease-specific mortality rate											
2	randomised trials	none	none	none	serious[2]	none	11/105 (10.5%)	14/105 (13.3%)	NR	-	MODERATE
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity											
0	No evidence										

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BCG**	**Chemotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**
	available										
Health-related quality of life											
0	No evidence available										

[1] *From meta-analysis in Sylvester et al. 2005; 2 Low number of events limits precision; 3 Confidence interval includes null value*

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Table 38: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: BCG versus MMC

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	MMC	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up median 26 months)											
12[1]	randomised trials	none	serious[2]	none	none	none	571/1467 (38.9%)	639/1374 (46.5%)	RR 0.77 (0.63 to 0.95)	107 fewer per 1000 (from 23 fewer to 172 fewer)	MODERATE
Recurrence - No BCG maintenance											
5[1]	randomised trials	none	serious[2]	none	serious[4]	none	261/640 (40.8%)	201/557 (36.1%)	RR 0.95 (0.72 to 1.25)	18 fewer per 1000 (from 101 fewer to 90 more)	LOW
Recurrence - BCG maintenance											
7[1]	randomised trials	none	serious[2]	none	None	none	287/781 (37.5%)	438/817 (53.6%)	RR 0.68 (0.55 to 0.83)	172 fewer per 1000 (from 91 fewer to 241 fewer)	MODERATE
Recurrence by risk and maintenance - Maintenance and high risk											
3[1]	randomised trials	none	serious[2]	none	None	none	144/352 (40.9%)	200/352 (56.8%)	RR 0.69 (0.5 to 0.96)	176 fewer per 1000 (from 23 fewer to 284 fewer)	MODERATE
Recurrence by risk and maintenance - Maintenance and intermediate risk											
3[1]	randomised trials	none	None	none	None	none	143/429 (33.3%)	215/419 (51.3%)	RR 0.59 (0.48 to 0.73)	210 fewer per 1000 (from 139 fewer to 267 fewer)	HIGH
Recurrence by risk and maintenance - No maintenance and high risk											
1[1]	randomised trials	none	None	none	serious[3,4]	none	19/31 (61.3%)	24/30 (80%)	RR 0.77 (0.55 to 1.07)	184 fewer per 1000 (from 360 fewer to 56 more)	MODERATE
Recurrence by risk and maintenance - No maintenance and intermediate risk											
4[1]	randomised trials	none	serious[2]	none	serious[4]	none	242/609 (39.7%)	177/527 (33.6%)	RR 1.01 (0.75 to 1.37)	3 more per 1000 (from 84 fewer to 124 more)	LOW
Progression (follow-up median 26 months)											
9[5]	randomised trials	none	None	none	serious[3,4]	none	98/1277 (7.7%)	107/1133 (9.4%)	RR 0.79 (0.61 to 1.03)	20 fewer per 1000 (from 37 fewer to 3 more)	MODERATE
Progression - No BCG Maintenance											
4[5]	randomised trials	none	None	none	serious[3,4]	none	30/609 (4.9%)	21/527 (4%)	RR 1.15 (0.67 to 2)	6 more per 1000 (from 13 fewer to 40 more)	MODERATE
Progression - BCG maintenance											
5[5]	randomised trials	none	None	none	serious[3]	none	68/668 (10.2%)	86/606 (14.2%)	RR 0.7 (0.52 to 0.94)	43 fewer per 1000 (from 9 fewer to 68 fewer)	MODERATE

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Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	MMC	Relative (95% CI)	Absolute	Quality
Time to first recurrence (Malmstrom IPD) (follow-up median 4.4 years)											
9[6]	randomised trials	none	serious[2]	none	serious[4]	none	616/1437 (42.9%)	600/1383 (43.4%)	HR 0.91 (0.81 to 1.02)	30 fewer per 1000 (from 65 fewer to 6 more)	LOW
Time to first recurrence - No BCG maintenance											
4[6]	randomised trials	none	None	none	None	none	309/726 (42.6%)	245/770 (31.8%)	HR 1.28 (1.07 to 1.52)	69 more per 1000 (from 18 more to 123 more)	HIGH
Time to first recurrence - BCG maintenance											
5[6]	randomised trials	none	None	none	None	none	307/711 (43.2%)	355/613 (57.9%)	HR 0.68 (0.58 to 0.8)	134 fewer per 1000 (from 80 fewer to 184 fewer)	HIGH
Progression (Malmstrom IPD) (follow-up median 4.8 years)											
7[6]	randomised trials	none	None	none	serious[3,4]	none	114/1050 (10.9%)	110/830 (13.3%)	RR 0.82 (0.64 to 1.05)	24 fewer per 1000 (from 48 fewer to 7 more)	MODERATE
Overall mortality rate (follow-up median 4.8 years)											
7[6]	randomised trials	none	None	none	serious[4]	none	213/1437 (14.8%)	234/1383 (16.9%)	RR 0.88 (0.74 to 1.04)	20 fewer per 1000 (from 44 fewer to 7 more)	MODERATE
Disease-specific mortality rate (follow-up median 4.8 years)											
7[6]	randomised trials	none	None	none	serious[3,4]	none	59/1437 (4.1%)	77/1383 (5.6%)	RR 0.74 (0.53 to 1.03)	14 fewer per 1000 (from 27 fewer to 2 more)	MODERATE
Treatment-related morbidity (assessed with: Rate of cystitis)											
5[1]	randomised trials	none	None	none	None	none	485/901 (53.8%)	304/776 (39.2%)	RR 1.37 (1.25 to 1.5)	145 more per 1000 (from 98 more to 196 more)	HIGH
Treatment-related morbidity (assessed with: Rate of fever)											
2[1]	randomised trials	none	none	none	serious[3]	none	56/324 (17.3%)	11/332 (3.3%)	RR 5.20 (2.78 to 9.74)	139 more per 1000 (from 59 more to 290 more)	MODERATE
Treatment-related mortality (assessed with: Sepsis, death)											
5[1]	randomised trials	none	none	none	serious[3]	none	0/901 (0%)	0/776 (0%)	-	-	MODERATE
Health-related quality of life											
0	No evidence										

[1] From meta-analyses in Bohle et al.(2003); [2] Significant statistical heterogeneity; [3] Small number of events limits precision; [4] Confidence intervals include null value; [5] From meta-analysis in Bohle & Bock 2004 [6] From meta-analysis in Malmstrom et al. 2009

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Table 39: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: BCG versus Epirubicin

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	Epirubicin	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up 33 to 110 months)											
5[1]	randomised trials	serious[2]	none	none	none	none	195/549 (35.5%)	289/562 (51.4%)	RR 0.69 (0.6 to 0.79)	159 fewer per 1000 (from 108 fewer to 206 fewer)	MODERATE
Recurrence - Connaught BCG											
1	randomised trials	serious[2]	none	none	serious[3]	none	30/102 (29.4%)	59/107 (55.1%)	RR 0.53 (0.38 to 0.75)	259 fewer per 1000 (from 138 fewer to 342 fewer)	LOW
Recurrence - Pasteur BCG											
2	randomised trials	serious[2]	none	none	serious[3,4]	none	36/108 (33.3%)	49/115 (42.6%)	RR 0.78 (0.56 to 1.1)	94 fewer per 1000 (from 187 fewer to 43 more)	LOW
Recurrence - Tice BCG											
2	randomised trials	None	none	none	None	none	129/339 (38.1%)	181/340 (53.2%)	RR 0.72 (0.6 to 0.85)	149 fewer per 1000 (from 80 fewer to 213 fewer)	HIGH
Progression											
5	randomised trials	serious[2]	none	none	serious[3,4]	none	44/549 (8%)	58/562 (10.3%)	RR 0.78 (0.54 to 1.13)	23 fewer per 1000 (from 47 fewer to 13 more)	LOW
Overall mortality (follow-up 3 to 127 months)											
2	randomised trials	None	none	none	serious[3,4]	none	125/383 (32.6%)	147/386 (38.1%)	RR 0.86 (0.71 to 1.04)	53 fewer per 1000 (from 110 fewer to 15 more)	MODERATE
Disease-specific mortality											
2	randomised trials	None	serious[5]	none	serious[3,4]	none	22/383 (5.7%)	26/386 (6.7%)	RR 0.94 (0.23 to 3.8)	4 fewer per 1000 (from 52 fewer to 189 more)	LOW
Local adverse effects, Drug induced cystitis											
4	randomised trials	None	serious[5]	none	None	none	232/429 (54.1%)	140/441 (31.7%)	RR 1.92 (1.38 to 2.65)	292 more per 1000 (from 121 more to 524 more)	MODERATE
Local adverse effects, Haematuria											
4	randomised	None	None	none	serious[3]	none	132/429	71/440	RR 1.9 (1.47	145 more per 1000	MODERATE

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BCG**	**Epirubicin**	**Relative (95% CI)**	**Absolute**	**Quality**
	trials						(30.8%)	(16.1%)	to 2.45)	(from 76 more to 234 more)	
Systemic adverse events											
3	randomised trials	None	serious[5]	none	serious[3]	none	134/385 (34.8%)	5/393 (1.3%)	RR 18.01 (2.25 to 143.91)	216 more per 1000 (from 16 more to 1000 more)	LOW
Delayed or terminated treatment due to adverse effects											
4	randomised trials	None	none	none	serious[3,4]	none	40/431 (9.3%)	33/441 (7.5%)	RR 0.91 (0.41 to 2.04)	7 fewer per 1000 (from 44 fewer to 78 more)	MODERATE
Treatment-related mortality											
0	No evidence										
Health-related quality of life											
0	No evidence										

[1] From meta-analysis in Shang et al. 2011; [2] Three trials were quasi-randomised by date of birth. Only one trial used good allocation concealment methods. The other 4 trials did not provide information on randomisation and allocation concealment; [3] Small number of events limits precision; [4] Confidence interval includes null value; [5] Statistical heterogeneity between studies

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Table 40: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: BCG versus Gemcitabine

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	GEM	Relative (95% CI)	Absolute	Quality
Recurrence - intermediate risk (follow-up mean 10.8 months)											
1[1]	randomised trials	serious[2]	none	none	serious[3,4]	none	12/40 (30%)	10/40 (25%)	RR 1.2 (0.59 to 2.45)	50 more per 1000 (from 103 fewer to 363 more)	LOW
Progression - intermediate risk (follow-up mean 10.8 months)											
1[1]	randomised trials	serious[2]	none	none	serious[5]	none	NR	NR	No significant difference	-	LOW
Toxicity – Dysuria											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	14/40 (35%)	5/40 (12.5%)	RR 2.8 (1.11 to 7.04)	225 more per 1000 (from 14 more to 755 more)	LOW
Toxicity - Urinary frequency											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	18/40 (45%)	4/40 (10%)	RR 4.5 (1.67 to 12.12)	350 more per 1000 (from 67 more to 1000 more)	LOW
Recurrence - high risk (follow-up mean 44 months)											
1[6]	randomised trials	none	none	none	serious[3,4]	none	9/32 (28.1%)	17/32 (53.1%)	RR 0.53 (0.28 to 1.01)	250 fewer per 1000 (from 382 fewer to 5 more)	MODERATE
Progression - high risk (follow-up mean 44 months)											
1[6]	randomised trials	none	none	none	serious[3]	none	0/32 (0%)	0/32 (0%)	not pooled	not pooled	MODERATE
Local toxicity – cystitis											
1[6]	randomised trials	none	none	none	serious[3,4]	none	4/32 (12.5%)	3/32 (9.4%)	RR 1.33 (0.32 to 5.49)	31 more per 1000 (from 64 fewer to 421 more)	MODERATE
Systemic toxicity – fever											
1[6]	randomised trials	none	none	none	serious[3,4]	none	2/32 (6.3%)	0/32 (0%)	RR 5 (0.25 to 100.21)	-	MODERATE
Overall survival											
0	No evidence										
Disease-specific survival											
0	No evidence										
Treatment-related mortality											
0	No evidence										
Health-related quality of life											

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Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	GEM	Relative (95% CI)	Absolute	
0	No evidence										

[1] Bendary 2011 (as cited in Jones et al. 2012); [2] Randomisation method not reported. No blinding of intervention or outcome assessment. Short follow-up; [3] Small number of events; [4] Confidence interval includes null value; [5] Number of events not reported - likely to be low number; [6] Porena 2010

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Table 41: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: Maintenance BCG versus induction BCG

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Maintenance BCG	Induction BCG	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up 16 to 84 months)											
5[1]	randomised trials	none	none	none	none	none	129/343 (37.6%)	185/343 (53.9%)	RR 0.7 (0.6 to 0.81)	162 fewer per 1000 (from 102 fewer to 216 fewer)	HIGH
Progression											
5[2]	randomised trials	none	none	none	serious[3]	none	102/369 (27.6%)	117/368 (31.8%)	RR 0.87 (0.71 to 1.06)	41 fewer per 1000 (from 92 fewer to 19 more)	MODERATE
Overall mortality											
3[4]	randomised trials	none	none	none	serious[3]	none	94/281 (33.5%)	103/280 (36.8%)	RR 0.91 (0.73 to 1.13)	33 fewer per 1000 (from 99 fewer to 48 more)	MODERATE
Disease-specific mortality											
2[5]	randomised trials	none	none	none	serious[3]	none	3/89 (3.4%)	3/88 (3.4%)	RR 0.99 (0.23 to 4.3)	0 fewer per 1000 (from 26 fewer to 113 more)	MODERATE
Treatment-related morbidity – dysuria											
2[6]	randomised trials	none	none	none	serious[7]	none	56/63 (88.9%)	43/63 (68.3%)	RR 1.3 (1.08 to 1.57)	205 more per 1000 (from 55 more to 389 more)	MODERATE
Treatment-related morbidity - fever/chills											
2[6]	randomised trials	none	none	none	serious[7]	none	25/63 (39.7%)	17/63 (27%)	RR 1.47 (0.88 to 2.44)	127 more per 1000 (from 32 fewer to 389 more)	MODERATE
Treatment-related mortality											
1[8]	randomised trials	none	none	none	serious[3]	none	2/192 (1%)	0/192 (0%)	RR 5 (0.24 to 103.47)	-	MODERATE
Health-related quality of life (measured with: EORTC QLQ-C30)											
1[9]	randomised trials	none	none	none	serious[10]	none	No change in QoL	No change in QoL	-		MODERATE
Health-related quality of life (assessed with: Proportion of patients with good overall Quality of life)											
1[11]	observational studies	none	none	none	serious[10]	none	48%	15%	-	-	VERY LOW

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[1] Hudson et al. 1987; Lamm et al. 2000; Palou 2001; Hinotsu et al. 2011; Koga et al. 2010; [2] Badalament et al..1987; Hinotsu et al. 2011; Koga et al. 2010; Palou 2001; Lamm et al. 2000; [3] Low number of events/ confidence interval includes null value; [4] Koga et al. 2010; Lamm et al. 2000; Palou 2001; [5] Koga et al. 2010; Palou 2001; [6] Hinotsu et al. 2011; Hudson et al. 1987; [7] Low number of events; [8] Lamm et al. 2000; [9] Koga et al. 2010; [10] Small sample size; [11] Mack 1996

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Table 42: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: Standard dose BCG (81mg) versus reduced dose BCG (27mg)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	81mg BCG	27mg BCG	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up median 65 months)											
2[1]	randomised trials	none	None	none	serious[2,3]	none	103/334 (30.8%)	109/320 (34.1%)	RR 0.9 (0.72 to 1.12)	34 fewer per 1000 (from 95 fewer to 41 more)	MODERATE
Progression (follow-up median 65 months)											
2[1]	randomised trials	none	None	none	serious[2,3]	none	49/334 (14.7%)	52/320 (16.3%)	RR 0.89 (0.62 to 1.27)	18 fewer per 1000 (from 62 fewer to 44 more)	MODERATE
Overall mortality											
2[1]	randomised trials	none	None	none	serious[2,3]	none	75/334 (22.5%)	76/320 (23.8%)	RR 0.94 (0.71 to 1.24)	14 fewer per 1000 (from 69 fewer to 57 more)	MODERATE
Disease-specific mortality											
2[1]	randomised trials	none	None	none	serious[2,3]	none	30/334 (9%)	29/320 (9.1%)	RR 0.98 (0.6 to 1.59)	2 fewer per 1000 (from 36 fewer to 53 more)	MODERATE
Treatment-related mortality											
2[1]	randomised trials	none	None	none	serious[2]	none	0/334 (0%)	0/320 (0%)	not pooled	not pooled	MODERATE
Any grade local toxicity											
2[1]	randomised trials	none	None	none	None	none	225/334 (67.4%)	170/320 (53.1%)	RR 1.27 (1.12 to 1.44)	143 more per 1000 (from 64 more to 234 more)	HIGH
Grade 3-4 Local toxicity											
2[1]	randomised trials	none	None	none	serious[2]	none	60/334 (18%)	24/320 (7.5%)	RR 2.38 (1.52 to 3.72)	104 more per 1000 (from 39 more to 204 more)	MODERATE
Any grade systemic toxicity											
2[1]	randomised trials	none	None	none	serious[2]	none	93/334 (27.8%)	42/320 (13.1%)	RR 2.15 (1.55 to 2.98)	151 more per 1000 (from 72 more to 260 more)	MODERATE
Grade 3-4 systemic toxicity											
2[1]	randomised trials	none	None	none	serious[2,3]	none	9/334 (2.7%)	12/320 (3.8%)	RR 0.74 (0.32 to 1.69)	10 fewer per 1000 (from 26 fewer to 26 more)	MODERATE
Health-related quality of life											
0	No evidence										

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**81mg BCG**	**27mg BCG**	**Relative (95% CI)**	**Absolute**	**Quality**
	available										

[1] *Martinez-Pineiro et al. 2002; 2005;* [2] *Low number of events limits precision;* [3] *Confidence interval includes null value*

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Table 43: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: Low dose BCG (27mg) versus very low dose BCG (13.5mg)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	27mg BCG	13.5mg BCG	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up 0-114 months)											
1[1]	randomised trials	none	None	none	serious[2,3]	none	38/142 (26.8%)	50/139 (36%)	RR 0.74 (0.52 to 1.06)	94 fewer per 1000 (from 173 fewer to 22 more)	MODERATE
Progression (follow-up 0-114 months)											
1[1]	randomised trials	none	None	none	serious[2,3]	none	14/142 (9.9%)	18/139 (12.9%)	RR 0.76 (0.39 to 1.47)	31 fewer per 1000 (from 79 fewer to 61 more)	MODERATE
Cancer-specific mortality (follow-up 0-114 months)											
1[1]	randomised trials	none	None	none	serious[2,3]	none	3/142 (2.1%)	5/139 (3.6%)	RR 0.59 (0.14 to 2.41)	15 fewer per 1000 (from 31 fewer to 51 more)	MODERATE
Overall mortality (follow-up 0-114 months)											
1[1]	randomised trials	none	None	none	serious[2,3]	none	13/142 (9.2%)	17/139 (12.2%)	RR 0.75 (0.38 to 1.48)	31 fewer per 1000 (from 76 fewer to 59 more)	MODERATE
Grade 3-4 Local toxicity											
1[1]	randomised trials	none	None	none	serious[2,3]	none	20/142 (14.1%)	10/139 (7.2%)	RR 1.96 (0.95 to 4.03)	69 more per 1000 (from 4 fewer to 218 more)	MODERATE
Grade 3-4 systemic toxicity											
1[1]	randomised trials	none	None	none	serious[2,3]	none	5/142 (3.5%)	3/139 (2.2%)	RR 1.63 (0.4 to 6.7)	14 more per 1000 (from 13 fewer to 123 more)	MODERATE
Any grade local toxicity											
1[1]	randomised trials	none	None	none	serious[2,3]	none	93/142 (65.5%)	89/139 (64%)	RR 1.02 (0.86 to 1.22)	13 more per 1000 (from 90 fewer to 141 more)	MODERATE
Any grade systemic toxicity											
1[1]	randomised trials	none	None	none	serious[2,3]	none	16/142 (11.3%)	15/139 (10.8%)	RR 1.04 (0.54 to 2.03)	4 more per 1000 (from 50 fewer to 111 more)	MODERATE
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence										

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**27mg BCG**	**13.5mg BCG**	**Relative (95% CI)**	**Absolute**	**Quality**
	available										

[1] *Ojea et al. 2007;* [2] *Low number of events;* [3] *Confidence interval includes null value*

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Table 44: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: Standard dose BCG (81mg) versus reduced dose BCG (27mg)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	81mg BCG	27mg BCG	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up median 7.1 years)											
1[1]	randomised trials	none	None	none	serious[2]	none	276/677 (40.8%)	311/678 (45.9%)	RR 0.89 (0.79 to 1.00)	50 fewer per 1000 (from 96 fewer to 0 more)	MODERATE
Progression (follow-up median 7.1 years)											
1[1]	randomised trials	none	None	none	serious[2,3]	none	53/677 (7.8%)	56/678 (8.3%)	RR 0.95 (0.66 to 1.36)	4 fewer per 1000 (from 28 fewer to 30 more)	MODERATE
Overall mortality rate (follow-up median 7.1 years)											
1[1]	randomised trials	none	None	none	serious[2]	none	185/677 (27.3%)	184/678 (27.1%)	RR 1.01 (0.85 to 1.20)	3 more per 1000 (from 41 fewer to 54 more)	MODERATE
Disease-specific mortality rate (follow-up median 7.1 years)											
1[1]	randomised trials	none	None	none	serious[2,3]	none	38/377 (10.1%)	30/678 (4.4%)	RR 1.27 (0.80 to 2.02)	12 more per 1000 (from 9 fewer to 45 more)	MODERATE
Local or systemic adverse events											
1[1]	randomised trials	none	None	none	serious[2,3]	none	50/657 (7.6%)	53/659 (8%)	RR 0.95 (0.65 to 1.37)	4 fewer per 1000 (from 28 fewer to 30 more)	MODERATE
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Oddens et al. 2013 [2] Confidence interval includes null value [3] Low number of events

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Table 45: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: Standard dose BCG (81mg) versus reduced dose BCG (54mg)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	81mg BCG	54mg BCG	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up mean 33.5 months)											
1[1]	randomised trials	serious[2]	None	none	serious[3]	none	9/40 (22.5%)	16/40 (40%)	RR 0.56 (0.28 to 1.12)	176 fewer per 1000 (from 288 fewer to 48 more)	LOW
Progression (follow-up mean 33.5 months)											
1[1]	randomised trials	serious[2]	None	none	serious[3]	none	1/40 (2.5%)	2/40 (5%)	RR 0.5 (0.05 to 5.3)	25 fewer per 1000 (from 47 fewer to 215 more)	LOW
Treatment-related morbidity: Cystitis											
1[1]	randomised trials	serious[2]	None	none	serious[3]	none	24/40 (60%)	19/40 (47.5%)	RR 1.26 (0.84 to 1.91)	123 more per 1000 (from 76 fewer to 432 more)	LOW
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Yalcinkaya et al. 1998 [2] No details of randomisation method, allocation concealment, or blinding. Method and results of data analysis not reported. [3] Small number of events / confidence intervals include null value

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Table 46: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: 120mg BCG versus 80mg BCG versus 40mg BCG

Quality assessment							No of patients			Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A: 120mg BCG	B: 80mg BCG	C: 40mg BCG	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up mean 36 months)												
1[1]	randomised trials	serious[2]	None	none	serious[3]	none	8/40 (20%)	12/48 (25%)	8/40 (20%)	A versus B – RR 0.80 (0.36 to 1.76) A versus C – RR 1.00 (0.42 to 2.40) B versus C – RR 1.25 (0.57 to 2.75)	-	LOW
Progression (follow-up mean 36 months)												
1[1]	randomised trials	serious[2]	None	none	serious[3]	none	0/40 (0%)	0/48 (0%)	0/40 (0%)	-	-	LOW
Overall survival												
0	No evidence available											
Disease-specific survival												
0	No evidence available											
Treatment-related mortality												
0	No evidence available											
Local toxicity - Dysuria (follow-up mean 36 months)												
1[1]	randomised trials	serious[2]	None	none	serious[3]	none	28/40 (70%)	16/48 (33.3%)	12/40 (30%)	A versus B – RR 2.10 (1.34 to 3.29) A versus C – RR 2.33 (1.39 to 3.91) B versus C – RR 1.11 (0.60 to 2.07)	-	LOW
Systemic toxicity - Fever >38 C (follow-up mean 36 months)												
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	12/40 (30%)	0/48 (0%)	0/40 (0%)	A versus B – RR 29.88 (1.82 to 489.42) A versus C – RR 25 (1.53 to 408.39)	-	LOW

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Quality assessment							No of patients			Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A: 120mg BCG	B: 80mg BCG	C: 40mg BCG	Relative (95% CI)	Absolute	Quality
Health-related quality of life												
0	No evidence available											

[1] Agrawal et al. 2007; [2] Method of randomisation, allocation concealment not reported. Baseline characteristics of patients not reported; [3] Low number of events limits precision

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Table 47: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: One immediate instillation chemotherapy versus one instillation plus maintenance

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	One dose	One dose + maintenance	Relative (95% CI)	Absolute	Quality
Recurrence											
3[1]	randomised trials	serious[2]	None	none	none	none	179/446 (40.1%)	138/433 (31.9%)	Not pooled	-	MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity (assessed with: Treatment stopped due to severe cystitis)											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life (measured with: SF-36)											
0	No evidence available										

[1] From systematic review by Sylvester et al. 2008 [2] In two studies, patients who recurred at [3] mo prior to starting their additional instillations were already counted as having their first recurrence, potentially diluting the treatment effect size.

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Table 48: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: One immediate instillation followed by short-term versus long-term instillations during 12 months

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-term	Long-term	Relative (95% CI)	Absolute	Quality
Recurrence											
3[1]	randomised trials	none	None	none	serious[2]	none	156/443 (35.2%)	131/412 (31.8%)	not pooled	not pooled	MODERATE
Progression (follow-up median 48 months)											
1[3]	randomised trials	none	None	none	serious[2,4]	none	3/210 (1.4%)	7/185 (3.8%)	RR 0.38 (0.1 to 1.44)	23 fewer per 1000 (from 34 fewer to 17 more)	MODERATE
Treatment-related morbidity											
1[3]	randomised trials	none	None	none	serious[5]	none	NR	NR	-	-	MODERATE
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester et al. 2008 plus randomised trial in Serretta et al. 2010 [2] Low number of events [3] Serretta et al. 2010 [4] Confidence interval includes null value [5] Number of adverse events in each arm not reported. Authors state no significant differences in toxicity between groups

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Table 49: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: One immediate instillation chemotherapy versus delayed instillations to month 12

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**One immediate dose**	**Delayed instillations**	**Relative (95% CI)**	**Absolute**	**Quality**
Recurrence											
3[1]	randomised trials	none	none	none	serious[2]	none	73/242 (30.2%)	67/270 (24.8%)	RR 1.24 (0.93 to 1.66)	60 more per 1000 (from 17 fewer to 164 more)	MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester et al. 2008 [2] Small number of events / confidence interval includes null value

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Table 50: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: One immediate instillation chemotherapy + additional instillations during 6 mo versus delayed instillations during 6 mo

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose + 6mo instillations**	**Delayed instillations 6mo**	**Relative (95% CI)**	**Absolute**	**Quality**
Recurrence											
2[1]	randomised trials	serious[2]	None	none	none	none	179/398 (45%)	117/239 (49%)	not pooled	not pooled	MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester et al. 2008 [2] Immediate instillation not given on same day as TUR in one included study

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Table 51: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: One immediate instillation chemotherapy + additional instillations during 12 mo versus delayed instillations during 12 mo

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose+12mo instillations**	**Delayed instillations 12 mo**	**Relative (95% CI)**	**Absolute**	**Quality**
Recurrence											
3[1]	randomised trials	none	none	none	serious[2]	none	128/382 (33.5%)	138/402 (34.3%)	RR 0.97 (0.80 to 1.17)	10 fewer per 1000 (from 69 fewer to 58 more)	MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester et al. 2008 [2] Small number of events / confidence interval includes null value

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Table 52: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: Short-term delayed instillations versus long-term delayed instillations

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Delayed short-term**	**Delayed long-term**	**Relative (95% CI)**	**Absolute**	**Quality**
Recurrence											
10[1]	randomised trials	none	serious[2]	none	none	none	-	-	not pooled		MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester et al. 2008 [2] Contradictory results. Range of effects across studies.

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Table 53: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: Less intense or frequent schedule of chemotherapy versus more intense or frequent schedule of chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Less intense or frequent schedule**	**More intense or frequent schedule**	**Relative (95% CI)**	**Absolute**	**Quality**
Recurrence											
9[1]	randomised trials	none	serious[2]	none	none	none	-	-	not pooled		MODERATE
Progression											
0	No evidence available										
Overall survival											
0	No evidence available										
Disease-specific survival											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] From systematic review by Sylvester et al. 2008 [2] Range of doses and durations of schedules used across studies

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Table 54: GRADE evidence profile: What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: Intravesical chemotherapy + BCG versus maintenance BCG alone

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination therapy	BCG alone	Relative (95% CI)	Absolute	Quality
Recurrence											
5[1]	randomised trials	none	serious[2]	none	serious[3]	none	196/460 (42.6%)	204/437 (46.7%)	RR 0.92 (0.8 to 1.06)	37 fewer per 1000 (from 93 fewer to 28 more)	LOW
Recurrence – CIS											
2[1]	randomised trials	none	None	none	serious[3,4]	none	110/207 (53.1%)	91/193 (47.2%)	RR 1.13 (0.93 to 1.37)	61 more per 1000 (from 33 fewer to 174 more)	MODERATE
Recurrence - Ta/T1											
3[1]	randomised trials	none	None	none	serious[3,4]	none	86/253 (34%)	113/244 (46.3%)	RR 0.75 (0.61 to 0.92)	116 fewer per 1000 (from 37 fewer to 181 fewer)	MODERATE
Progression											
5[1]	randomised trials	none	serious[2]	none	serious[3,4]	none	51/460 (11.1%)	57/437 (13%)	RR 0.84 (0.59 to 1.2)	21 fewer per 1000 (from 53 fewer to 26 more)	LOW
Progression – CIS											
2[1]	randomised trials	none	serious[2]	none	serious[3,4]	none	36/207 (17.4%)	25/193 (13%)	RR 1.33 (0.83 to 2.13)	43 more per 1000 (from 22 fewer to 146 more)	LOW
Progression - Ta/T1											
3[1]	randomised trials	none	None	none	serious[4]	none	15/253 (5.9%)	32/244 (13.1%)	RR 0.45 (0.25 to 0.81)	72 fewer per 1000 (from 25 fewer to 98 fewer)	MODERATE
Overall survival											
0	No evidence										
Disease-specific survival											
0	No evidence										
Treatment-related morbidity											
3[1]	randomised trials	serious[2]	none	none	Serious[5]	none	-	-	-	-	LOW
Treatment-related mortality											
0	No evidence										
Health-related quality of life											
0	No evidence										

[1] From meta-analysis in Houghton et al. (2012) plus randomised trial reported in Oosterlinck et al. (2011); [2] Significant statistical heterogeneity; [3] Confidence interval includes null value; [4] Small number of events; [5] Number of events in each arm not reported in Houghton et al. 2012 and Oosterlinck et al. 2011. No difference in toxicity rate between combination therapy and BCG alone.

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Cost-effectiveness evidence (see also Appendix A)

Background

Non-muscle invasive bladder cancer (NMIBC) tumours can be surgically removed using transurethral resection of bladder tumour (TURBT). However, these tumours are likely to return on the urothelium. This high risk of recurrence is a problem for patients because it raises the concern that the cancer will progress and so the patient will need to undergo further treatment (either another TURBT or diathermy).

The risk of recurrence can be reduced by the administration of chemotherapy medication into the bladder (intravesical chemotherapy), which can be done immediately, or shortly after TURBT. However, there are disadvantages to using intravesical chemotherapy as it is associated with some side effects and comes at an additional cost.

Aim of analysis:

To estimate the cost-effectiveness of a single instillation of intravesical chemotherapy in addition to TURBT in comparison to TURBT alone in patients with NMIBC.

Existing Economic Evidence

A systematic literature review identified one paper related to the decision problem, a cost-utility analysis by Green et al. 2013. In the study, a decision analytic model was utilised to estimate the cost-effectiveness of fulguration compared to TURBTs with and without perioperative intravesical chemotherapy in patients with low risk NMIBC.

The authors concluded that fulguration without perioperative intravesical chemotherapy was the most cost-effective strategy for treating low-risk NMIBC. However, unusually, the authors based this conclusion upon individual cost-effectiveness calculations rather than the standard incremental calculations. When following the more standard cost-effectiveness methodology using incremental cost-effectiveness ratios (ICERs), it appears that perioperative intravesical chemotherapy plus fulguration would be the most cost-effective strategy. This strategy has an ICER of $4,169 per QALY, which is likely to fall below the cost-effectiveness threshold[a]. The authors also conducted sensitivity analysis, which showed that the effectiveness of perioperative intravesical chemotherapy and the cost of TURBT were likely to be key drivers of the cost-effectiveness result.

However, Green et al. 2013 can only be deemed partially applicable to the decision problem this guideline seeks to address. The analysis considered the US healthcare system, which differs substantially from the UK system. In addition, the study only partially addressed our decision problem as it only evaluated cost-effectiveness in low risk NMIBC patients, whereas we are interested in all NMIBC risk groups.

Overall, it was considered that the current economic literature was partially useful but further analysis would be required to robustly estimate the cost-effectiveness. It should also be noted that the existing economic literature was useful for informing the development of our own economic model.

De Novo Economic Model

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel.

[a] However, it should be noted that there is no official cost-effectiveness threshold used in the evaluation of treatments in the US health care system.

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The patient enters the model in a 'disease free' state following an initial transurethral resection of the bladder tumour (TURBT) with or without a single instillation of chemotherapy (depending upon modelled treatment arm). At each 3-monthly model cycle the patient may experience a bladder cancer recurrence. If the recurrence is detected, the patient will undergo a further TURBT (or fulguration of the tumour) and return to a disease free state. However, if the recurrence is not detected, then the patient will be at risk of progression and will have to undergo further treatment once this progression is eventually detected (cystectomy and possibly neo-adjuvant chemotherapy). The patient may also die from bladder cancer related mortality after experiencing progression and may die from other cause mortality from any health state.

Estimated total costs and quality adjusted life yefars (QALYs) are collected over the modelled 10 year time horizon for each follow-up strategy. Future costs and benefits were discounted at a rate of 3.5% per year as recommended by NICE.

The risk of recurrence and progression in patients with NMIBC was estimated using risk equations based on an analysis of 2,596 patients from seven EORTC[b] trials (Sylvester et al. 2006). Patients are 'scored' based on a number of risk factors, such as number of tumours, tumour size, prior recurrence rate, T category, presence of CIS and grade. An individual's one year and five year risks of recurrence and progression can then be estimated based upon these scores.

For the purposes of the economic model, it was necessary to convert these five year and one year risks into 3-monthly risks. The higher risk of recurrence and progression in the first year was captured by calculating separate 3 monthly risks for the first year and subsequent years (based on the one year risk and five year EORTC risks). Furthermore, since the EORTC risk equations consider recurrence and progression independently, it was necessary to link the progression rates to the recurrence rate i.e. estimate the probability of progression given recurrence in each of the risk groups (Table 55).

Table 55: Three monthly recurrence and progression risk applied in the model

Outcome	3 monthly rates		
	Recurrence	**Progression given recurrence**	**Progression**
First year			
Low risk	3.98%	1.26%	0.05%
Intermediate risk	6.63%	3.78%	0.25%
High risk – Lower	11.26%	11.31%	1.27%
High risk – Upper	20.97%	21.70%	4.55%
Subsequent years			
Low risk	1.84%*	2.18%*	0.04%*
Intermediate risk	3.03%	10.18%	0.31%
High risk – lower	4.72%	19.64%	0.93%
High risk – upper	7.29%	40.39%	2.94%

<Insert Note here>

As the modelled time horizon of 10 years exceeds the predicted risk estimates from the EORTC trials (5 years), it was also necessary to make some assumptions about the risk profile of patients in years 5-10. In the base case, it was assumed that the subsequent year rate (i.e. years 2-5) would be maintained in years 6-10 except in the case of low-risk patients in whom it was assumed that risk would be zero after 5 years (reflecting clinical practice of discharging low-risk patients from follow-up after 5 years).

[b] European Organisation for Research and Treatment of Cancer

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The key effectiveness data utilised in the model is the reduction in recurrence risk associated with a single instillation of intravesical chemotherapy following a TURBT. According to the systematic review of the clinical evidence, the use of a single instillation of intravesical chemotherapy in addition to TURBT has a relative risk of 0.67 in comparison to TURBT alone. This treatment effect was assumed to last for two years reflecting the general consensus around its possible duration. Thereafter, the risk of recurrence was assumed to be equal to that with TURBT only. In addition, the treatment effect is not assumed to affect future recurrences if the patient has a recurrence during the two years after the single chemotherapy instillation.

Note that the single instillation of chemotherapy does not directly reduce the rates of progression. This is in line with the evidence base, which suggests that there is no treatment effect on the rates of progression. However, it should be noted that because of the model structure, a lower rate of recurrences would lead to a lower rate of progression because progression is dependent upon recurrence. Therefore, an indirect treatment effect on progression is essentially included in the model. This assumption is relaxed in a sensitivity analysis where the rates of recurrence and progression are assumed to be independent.

No comparative data on morbidity were identified in the systematic review of the clinical evidence. However a meta-analysis (Sylvester 2004) of seven trials suggested that mild irritative bladder symptoms (including dysuria, frequency and macroscopic haematuria) would occur in approximately 10% of patients treated with a single post-operative dose of intravesical chemotherapy. In addition, allergic skin reactions were reported in 1-3% of patients in two studies.

Since no data were available on morbidity in patients treated with TURBT, it was conservatively assumed that 5% would have irritative bladder symptoms and there would be no skin reactions. The treatment related morbidity rates applied in the model are shown in the table below.

The diagnostic accuracy data for flexible cystoscopy were sourced from the systematic review of the clinical evidence conducted for this guideline, with most data being sourced from a systematic review by Mowatt et al. 2010.

Bladder cancer related mortality rates were estimated using data from a systematic review by Van den Bosch et al. 2011. Using the data in the study, separate three mortality rates were estimated for patients that progressed to muscle invasive disease and those that remained non-muscle invasive following a cystectomy (3.6% and 0.5%, respectively). The lower rate in NMIBC patients reflects an assumption that patients would have to first progress to MIBC before dying of bladder cancer.

Death from other causes was captured using 2009-2011 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender with the model assuming that 50% of patients were female and that the average age was 60 years old. These annual probabilities were converted to three-monthly probabilities for use in the model.

Costs and utilities

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. GP visit). Where possible, all costs were estimated in 2012-13 prices.

The majority of costs were sourced from NHS reference costs 2012/13 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dosages from the British National Formulary (BNF), and unit cost information from the electronic market information tool (eMit). Where unit costs for drugs were not available from eMit, prices from

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the BNF were used. Resource use and cost information were obtained from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs were estimated by combining the life year estimates with utility values (or QOL weights) associated with being in a particular health state. These utility values were identified through a search of the available literature.

Base case results

The base case results of the analysis are presented in table 56 for patients in each risk category. It can be seen that, in every risk category, a strategy of TURBT plus a single instillation of chemotherapy is more effective than a strategy of TURBT alone.

In the case of low and intermediate risk patients, it can also be seen that the addition of a single instillation of chemotherapy is cost saving over the modelled time horizon. This shows that the initial additional costs associated with the single chemotherapy instillation are outweighed by the cost savings associated with a reduction in recurrences (recurrence reductions of 17% and 10% were estimated over the modelled time horizon in the low and intermediate risk groups, respectively). Therefore in low and intermediate risk patients, a single instillation of chemotherapy can be considered dominant i.e. more effective and cost saving.

However, in the case of high risk patients, it can be seen that this is not the case. In high risk patients, the single instillation of chemotherapy is more costly than TURBT alone, suggesting that the potential cost savings are not as large in this group. However, it can also be seen that the addition of a single chemotherapy instillation provides an additional QALY at a cost of £6,432 and thus would be considered cost-effective using the NICE threshold (i.e. <£20,000 per QALY).

Table 56: Base case results of the model

Treatment strategy	Cost		QALYs		Cost per QALY
	Total	Incremental	Total	Incremental	
Low risk					
TUBRT alone	£8,850	-	6.29	-	-
TURBT + single chemo instillation	£8,203	-£647	6.30	0.0056	Dominant
Intermediate risk					
TUBRT alone	£21,992	-	6.20	-	-
TURBT + single chemo instillation	£21,191	-£801	6.22	0.0185	Dominant
High risk					
TUBRT alone	£27,679	-	5.52	-	-
TURBT + single chemo instillation	£28,069	£389	5.58	0.0605	£6,432

Sensitivity analysis

A series of one-way sensitivity analyses were conducted, whereby the value of an input parameter is changed and its effect on the overall outcome is recorded and assessed.

The analyses showed that the conclusion of the model is insensitive to changes in the input parameters over plausible ranges i.e. TURBT plus a single instillation of chemotherapy remains cost-effective in the all the analyses across all the risk groups.

The variations in the treatment effect duration are perhaps particularly notable as this is one of the uncertainties around the effectiveness of the single instillation of chemotherapy. The analysis shows, unsurprisingly, that the intervention is less cost-effective when the treatment effect duration is decreased. However, crucially, the single instillation of chemotherapy remains cost-effective in all analyses, even when making very pessimistic assumptions about

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the likely treatment effect duration (i.e. even when assuming that the chemotherapy instillation only reduces recurrences in the first 3 months after administration).

In addition to the core cost-utility analysis, the GDG were also interested in a cost analysis comparing the cost of delivering the single instillation of chemotherapy on the ward against the cost of delivering it in theatre. It was found that delivering the single instillation of chemotherapy in theatre was the cheaper of the two approaches (delivery by nurse estimated to cost an additional £23.83). This was primarily a result of the longer amount of time taken to deliver the instillation in the ward setting compared to in theatre.

A probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case were replaced with values drawn from distributions around the mean values. It was found that, at a threshold of £20,000 per QALY, TURBT plus a single instillation of chemotherapy has a very high probability of being cost-effective in the low and intermediate risk groups (100%). However, the probability is substantially lower in high risk patients at 66%, although still very much in favour of TURBT plus a single instillation of chemotherapy.

Conclusion

The results of the analysis suggest that the use of a single instillation of chemotherapy after a TURBT, in comparison to a TURBT alone, was found to be strongly cost-effective in all risk groups. It was found to be particularly cost-effective in low and intermediate risk groups, in which the strategy was cost saving as well as more effective (dominant). Furthermore, this result was found to be robust in alternative scenario analyses, one-way and probabilistic sensitivity analysis.

Recommendations	**Offer people with suspected bladder cancer a single dose of intravesical mitomycin C given at the same time as the first TURBT.** **Offer people with newly diagnosed intermediate-risk non-muscle-invasive bladder cancer a course of at least 6 doses of intravesical mitomycin C.** **If intermediate-risk non-muscle-invasive bladder cancer recurs after a course of intravesical mitomycin C, refer the person's care to a specialist urology multidisciplinary team.** **Offer induction and maintenance intravesical BCG to people having treatment with intravesical BCG.**
Relative value placed on the outcomes considered	The GDG considered progression to be an important outcome because it is associated with life-threatening complications and the need for more intensive treatment. Recurrence was also considered to be an important outcome because it leads to further treatment and patients noted the avoidance of recurrence as important. Treatment-related morbidity was considered important because intravesical therapy is associated with some side-effects. All of the outcomes from the PICO were reported by the evidence. No additional outcomes that were not specified in the PICO were used to make recommendations. The GDG considered that overall survival and disease-specific survival were not useful outcomes because there were no proven survival differences between treatments. Treatment-related mortality was not considered important because it is

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	not applicable to this patient group as intravesical therapy is not potentially lethal. Health-related quality of life outcomes were also not considered to be useful because very little evidence was identified and it was considered to be of poor quality.
Quality of the evidence	The quality of the evidence ranged from very low to high as assessed with GRADE. Some limitations with the evidence were highlighted. For example, there were issues with applicability to current UK practice because older therapy regimens were used in some studies (some data back to the 1970s) and some study populations were not applicable to the UK. The participants risk level was not clear in some of the included studies. Also, statistical heterogeneity was present in some of the published meta-analyses that were presented. The limitations with the evidence made it difficult for the GDG to make recommendations on specific subgroups. Because some of the chemotherapy regimens in the evidence are not used in current clinical practice the GDG chose to make recommendations based on current practice. The recommendation that the immediate chemotherapy instillation should be given at the time of TURBT (in theatre) was based, partly, on the GDG's experience. The GDG considered instillation at the time of TURBT to be more convenient for clinicians and patients. It also ensures that patients receive the full benefit of this time-dependent treatment. The patient representatives on the GDG were also strongly in favour of this recommendation. The referral to SMDT in patients with recurrent intermediate disease was also based on the GDG's experience. They felt that this was important to ensure a full range of treatment options are considered. Low quality economic evidence was identified. The economist highlighted that the study was only partially applicable to the decision problem as it considered a healthcare system other than the UK (US study). Also potentially serious limitations were identified with the study with uncertainty over some of the input parameters that were used in the model. In addition, the study interpreted the economic results using an atypical approach, leading to potential misleading conclusions i.e. different conclusions might be drawn when a more conventional approach is used. The analysis was also considered to be superseded by the de novo analysis conducted by the economist, which was directly applicable and followed the methodology advised by NICE. Therefore, the published analysis was not given much consideration by the GDG when drafting the recommendations as the de novo economic analysis conducted by the economist was considered to be more appropriate.
Trade-off between clinical benefits and harms	The GDG considered the main benefit of giving a single instillation of MMC to be a reduced risk of recurrence. Giving MMC in theatre should improve access to the treatment and be more convenient for patients. The benefits of giving MMC and BCG were thought to be a reduced risk of recurrence. For BCG there was also a reduced risk of progression.

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	The GDG compared the effectivenss of BCG and MMC and recognised that there maty be some benefit of BCG in reducing recurrence rates. However the extent of this benefit was unclear. In intermediate risk patients the GDG considered that the risk of progression were relatively low and so the reduced toxicity profile of mitomycin C was preferred. The GDG felt that referral to SMDT in patients with recurrent intermediate disease was important to ensure a full range of treatment options are considered. The GDG considered the potential harms of the recommendations made were the side-effects of intravesical treatment, particularly those associated with maintenance BCG. The GDG reached a consensus decision that many patients would rather endure the side-effects of treatment than have a cancer recurrence and receive surgical treatment.
Trade-off between net health benefits and resource use	A health economic model was developed for this topic. The results of the economic analysis were used to inform the recommendations made on the use of a single instillation of chemotherapy after an initial TURBT. The results showed that the addition of a single instillation of chemotherapy was cost-effective in all modelled risk groups. It was found to be particularly cost-effective in low and intermediate risk patients where TURBT + single chemotherapy instillation was found to be cheaper and more effective than TURBT alone (i.e. dominant)). In high risk patients, TURBT + single chemotherapy instillation was found to be more effective than TURBT alone but also more costly. However, it was shown to provide one additional QALY at a cost of £6,432, which is well below NICE's threshold of £20,000 per QALY and so it can therefore be considered cost-effective. While one-way sensitivity analysis demonstrated variation in the ICER values a single instillation of chemotherapy remained cost-effective in all modelled analyses. Furthermore, probabilistic sensitivity analysis showed that at, a threshold of £20,000 per QALY, a single instillation of chemotherapy has a very high probability of being cost-effective in the low and intermediate risk groups (100%). However, the probability is substantially lower in high risk patients at 66%, although still very much in favour of a single instillation of chemotherapy. The cost of delivering a single instillation in theatre was compared against the cost of later delivery by a nurse on the ward. Delivering it in theatre was found to be the cheaper of the two options (£23.83 cheaper). This was primarily a result of the shorter time taken by the urologist to deliver the drug in theatre. In the other areas of the topic not covered by the economic model, the GDG made the following considerations. Mitomycin C course The use of a course of mitomycin C was thought to be associated with increased costs because of the mitomycin C drug costs and the cost of treating side effects. However, there may also be potential cost savings from reduced recurrences and progression (and the further treatments that they

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	entail). Maintenance BCG The use of maintenance BCG was thought to be associated with increased costs because of the BCG drug costs and the cost of treating side effects. However, there may also be potential cost savings from reduced recurrences and progression (and the further treatments that they entail).
Other considerations	The GDG identified no equalities issues for this topic. The GDG considered that the recommendations reflect what is currently considered best practice but there is concern that this is not universally followed. The GDG noted that there may be some additional training required to perform the procedures recommended. The GDG expect to see an increased use of single instillation MMC, MMC course and BCG maintenance. There may also be an increase in referral to SMDT following MMC failure. The GDG anticipate that there will be a greater acceptance of the need to give intravesical MMC in theatre. Regarding the recommendation of referral to SMDT following MMC failure, the GDG discussed the possibility of recommending BCG for these patients. The GDG were mindful of existing NICE guidance (Improving Outcomes in Urological Cancers) and were mindful to ensure that best practice will be universally adopted.

4.2.2 The role of biopsy in people with recurrent non-muscle invasive bladder cancer

People with non-muscle invasive bladder cancer generally have regular cystoscopic follow up to identify recurrent cancer. The likely nature of any recurrence will depend on the nature of the previous cancer.

Treatment of low risk bladder cancer recurrences is generally by transurethral resection to remove the cancer or fulguration by either electrocautery or laser energy to destroy the cancer (with or without biopsy). The former allows pathological evaluation of the cancer and may be necessary to remove tissue from large cancers, but requires regional or general anaesthesia and a rigid cystoscopy and bladder resection. Consequently, the risks of intervention are higher than for fulguration (which may be performed under local anaesthesia). However, fulguration without biopsy does not obtain tissue for analysis and could miss the minority of cases in which the cancer is becoming more aggressive. This approach is less effective at removing the cancer and so could lead to higher recurrence (or residual cancers) rates and more post-treatment symptoms.

It is likely that there is significant variation in the use of risk classification in people with non-muscle invasive bladder cancer. There is also variation in whether or not biopsy is done for apparently low risk disease. Whilst it should be standard practice to biopsy any recurrence in people with intermediate or high risk non-muscle invasive bladder cancer, the variation in the use of risk classification means that this may not always occur.

Clinical question: In patients with recurrent bladder cancer and previous low risk bladder cancer does treatment without histological sampling affect outcome?

Clinical evidence (see also full evidence review)

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Evidence was provided by seven observational studies, only one of which was a comparative study. The evidence is summarised in table 57.

Evidence statements

Very low quality evidence from one retrospective observational study reported on 42 patients who underwent fulguration for recurrent Ta bladder cancer and 42 matched patients who underwent TURBT. 12 patients in the fulguration group and 11 patients in the TURBT group had a recurrence during follow-up (RR 0.92, 95% CI 0.46 to 1.84) (Park *et al.*, 2013).

Very low quality evidence from one prospective cohort study of outpatient laser ablation (OLA) in an elderly population (n=54) reported that the procedure was well tolerated with pain scores of 0-2 out of 10. The 3-month recurrence rate was 10.6% with white light OLA and 4.3% with PDD OLA (Wong *et al.*, 2013).

One study of electromotive drug administration (EMDA) of local anaesthetic (LA) for outpatient flexible cystoscopy biopsy and cystodiathermy of recurrent low grade pTaG1-2 (Biers & Mostafid 2009) reported that there were no recurrences at the site of cystodiathermy and there were no progression events. 19% (3/16) of those with benign pathology at biopsy had a recurrence after a mean follow-up of 16.4 months. 9% (1/11) of those with TCC pathology at biopsy had a recurrence, with a time to recurrence of 15 months. Mean pain score was one, on a scale of one (no pain) to 10 (worst pain). There were no intraoperative complications (Very low quality evidence).

One study of 48 patients who were suitable for cystodiathermy under LA reported a local recurrence rate of 6% (n=3) and 15 recurrences (31%) at a different site after a median of 15 weeks follow-up (80% subsequently treated with LA cystodiathermy and 20% referred for GA cystodiathermy). No progressions were reported (Davenport *et al.*, 2010) (Very low quality evidence).

Two studies of 192 patients (515 tumours) undergoing treatment for NMIBC recurrences with Ho:YAG laser ablation under LA with a flexible cystoscope reported a local recurrence rate of 12% (37/304) and an off-site recurrence rate of 50% (Syed *et al.* 2001; 2013). One study (Syed *et al.*, 2013) reported complication rates of dysuria (4.2%), frequency (1.5%), haematuria (1.9%) and no UTIs. Mean visual pain score was one, on a scale of 0 (no pain) to 10 (worst pain) (Very low quality evidence).

In one study of 267 patients, 103 had small, low grade papillary recurrence and negative cytology and underwent cystodiathermy at least once during the study period (Donat *et al.*, 2004). No significant differences were seen in progression of disease for patients undergoing cystodiathermy (n=103) compared to those never fulgurated in the office (n=164) (p=0.86) (Very low quality evidence).

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Table 57: GRADE evidence profile: In patients with recurrent bladder cancer and previous low risk bladder cancer does treatment with histological sampling versus treatment without histological sampling (e.g. cystodiathermy)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Histological sampling	Cystodiathermy	Relative (95% CI)	Absolute	Quality
Recurrence rate (TURBT versus Fulguration) (follow-up median 27.8 and 25.1 months)											
1[1]	observational studies	none	none	none	serious[2]	none	11/42 (26.2%)	12/42 (28.5%)	RR 0.92 (0.46 to 1.84)		VERY LOW
Recurrence rate at 3 months (outpatient laser ablation (OLA) without PDD versus OLA with PDD)											
1[3]	observational studies	none	none	none	serious[2]	none	10.6%	4.3%	-	-	VERY LOW
Recurrence rate (EDMA LA biopsy and cystodiathermy), Subgroup: No pathology possible (follow-up mean 12.7 months)											
1[4]	observational studies	none	none	none	serious[2]	none	0/6 (0%)	-	-	-	VERY LOW
Recurrence rate (EDMA LA biopsy and cystodiathermy), Subgroup: Benign pathology (follow-up mean 16.4 months)											
1[4]	observational studies	none	none	none	serious[2]	none	16/27 (59.3%)	-	-	-	VERY LOW
Recurrence rate (EDMA LA biopsy and cystodiathermy), Subgroup: TCC pathology											
1[4]	observational studies	none	none	none	serious[2]	none	1/11 (9.1%)	-	-	-	VERY LOW
Local recurrence rate (cystodiathermy) (assessed by: recurrence at same site treated by cystodiathermy; follow-up mean 15 weeks)											
1[5]	observational studies	none	none	none	serious[2]	none	-	3/48 (6.3%)	-	-	VERY LOW
Recurrence at untreated area (cystodiathermy) (follow-up mean 15 weeks)											
1[5]	observational studies	none	none	none	serious[2]	none	-	15/48 (31.3%)	-	-	VERY LOW
Local recurrence rate (Ho:YAG laser) (assessed by: recurrence at treated site)											
2[6]	observational studies	none	none	none	serious[2]	none	-	37/304 (12.2%)	-	-	VERY LOW
Recurrence at untreated area (Ho:YAG laser)											
2[6]	observational studies	none	none	none	serious[2]	none	-	111/222 (50%)	-	-	VERY LOW
Progression (follow-up median 2.6 years; assessed with: Increase in clinical stage or metastases)											
1[7]	observational studies	none	none	none	serious[8]	none	N=164	N=103	(p=0.860)[9]		VERY LOW
Residual tumour rate											
0	No evidence available										
Treatment-related morbidity EDMA LA biopsy and cystodiathermy (assessed with: Median pain score, scale 0 (no pain) to 10 (worst pain))											

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Histological sampling**	**Cystodiathermy**	**Relative (95% CI)**	**Absolute**	**Quality**
1[4]	randomised trials	none	none	none	serious[2]	none	Mean score =1	-	-	-	VERY LOW
Treatment-related morbidity Ho:YAG laser (assessed with: Dysuria, frequency, haematuria, microbiological UTIs)											
1[10]	observational studies	none	none	none	serious[2]	none	-	4.2% dysuria, 1.5% frequency, 1.9% haematuria, 0 UTIs	-	-	VERY LOW
Treatment-related morbidity (outpatient laser ablation) (assessed with pain score, scale 0 (no pain) to 10 (worst pain)											
1[3]	observational studies	none	none	none	serious[2]	none		Pain score 0-2 in all 54 patients			VERY LOW
Health related quality of life											
0	No evidence available										

[1] Park et al. 2013 [2] Low number of events limits precision. [3] Wong et al. 2013 [4] Biers et al. 2009 [5] Davenport et al. 2010 [6] Syed et al. 2001; Syed et al. 2013 [7] Donat et al. 2004 [8] Small sample size limits precision. Number of events not reported. [9] No differences in progression for cystodiathermy versus those never fulgurated in office [10] Syed et al. 2013

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Cost-effectiveness evidence

The primary results of the analyses by Green et al. 2013 and Wong et al. 2013 are summarised in table 58.

Green et al. 2013 concluded that fulguration without perioperative intravesical chemotherapy was the most cost-effective strategy for treating low-risk NMIBC. However, unusually, the authors based this conclusion upon individual cost-effectiveness calculations rather than the standard incremental calculations. When following the more standard cost-effectiveness methodology using incremental cost-effectiveness ratios (ICERs), the strategy of perioperative intravesical chemotherapy plus fulguration would most likely be considered the most cost-effective strategy with an ICER of $4,169 per QALY.

Of particular relevance to the topic at hand, was the finding that fulguration was more cost-effective than TURBT when both were used alone or when both were used in combination with intravesical chemotherapy. In both instances fulguration was found to be more effective and cheaper than TURBT alone i.e. dominant. However, as the study is US based, these results may lack applicability to the UK healthcare system.

Wong et al. 2013 found that outpatient laser ablation was cost-effective in comparison to inpatient cystodiathermy for the treatment of NMIBC, especially in elderly patients. In the base case, outpatient laser ablation was found to be cheaper (cost reduction of $2,526) and more effective (0.12 QALYs) than inpatient cystodiathermy and is thus dominant. A further analysis showed that using PDD in addition to outpatient laser ablation was also cost-effective and indeed dominant in comparison to inpatient cystodiathermy.

Probabilistic sensitivity analysis showed that, at a threshold of £30,000 per QALY, outpatient laser ablation had approximately an 80%[c] probability of being cost-effective in comparison to intravesical chemotherapy. With the addition of PDD to OLA, the strategy was more cost-effective than IC in 79.2% of simulations.

However, while the study is of some interest, it does not directly address the decision problem at hand because TURBT is not used as a comparator. The study instead compares two alternatives to TURBT and thus the key aspect of our decision problem remains unanswered by this study.

While both of these studies are somewhat useful, their lack of direct applicability to the decision problem under consideration makes it difficult to draw firm conclusions. As such, the cost-effectiveness of perioperative intravesical chemotherapy remains, to a large extent, uncertain.

[c] Note that an approximate figure is used as two figures are presented for cost-effectiveness probability in the study (81.49% and 84.1%).

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Table 58: Modified GRADE table showing the included evidence (Green et al. 2013 and Wong et al. 2013) for the treatment of recurrent bladder cancer and previous low risk bladder cancer with and without histological sampling

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Green et al. 2013	Hypothetical cohort of patients with low-risk NMIBC after the initial transurethral resection of bladder tumour (TURBT).	Full results						A series of one-way and two-way sensitivity analyses were conducted. PIC + fulguration and fulguration alone were cost-effective in most analyses. PIC + fulguration and fulguration alone were co-dominant until annual recurrence increased to ≥14.2%, at which point fulguration alone was singularly dominant. PIC + fulguration became more cost-efficient than fulguration alone when total PIC costs moved towards zero. Strategies involving TURBT only cost-effective when the cost of TUBRT < $1175.	Partially applicable as it considered the US health care system, which differs substantially from the UK system. Some potentially serious limitations were identified, including uncertainty over the treatment effect and an unusual interpretation of the cost-effectiveness results.
		No PIC (perioperative intravesical chemotherapy) + fulguration	$9,404.61	14.36	-	-	-		
		PIC + fulguration	$9,972.95	14.50	$568.34	0.14	$4,169.24		
		No PIC + TURBT	$10,641.23	14.34	$668.28	-0.16	Dominated		
		PIC + TURBT	$10,907.36	14.48	$934.41	-0.02	Dominated		

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Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
								PSA was not conducted.	
	Comments: Interventions are listed in dominance rank format.								
Wong et al. 2013	Patients with NMIBC that are elderly and frail or have multiple co-morbidities.	Inpatient cystodiathermy (IC)	£5,744.33	3.56 QALYs	Reference			One-way sensitivity analysis was conducted on the time horizon modelled. OLA was found to remain dominant when a 5 year time horizon or lifetime horizon was adopted. A further analysis considered the addition of PDD to OLA. OLA plus PDD was found to be dominant in comparison to IC. PSA was conducted. At a threshold of £30,000 per QALY, OLA was more cost-effective than IC in 81.49% or 84.1% of simulations (two values reported in study). With the addition of PDD to OLA, the strategy was more cost-effective than	Partially applicable because of uncertainty over the applicability of some model inputs (QoL values and discount rates), details of which were omitted in the report. In addition, the objective of the analysis is only partly applicable to our decision problem . Serious limitations were also identified with omissions in the study report making it difficult to assess the quality of many of the input parameters applied in the model.
		Outpatient (office based) local anaesthetic (OLA)	£3,217.96	3.68 QALYs	-£2,526	0.12	OLA is dominant (more effective and cheaper)		

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Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
								IC in 79.2% of simulations.	
	Comments: Numerous omissions in the reporting of the study make it difficult to fully appraise the applicability and quality of the economic evaluation								

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Recommendations	**Consider fulguration without biopsy for people with recurrent non-muscle-invasive bladder cancer if they have all of the following:** • **no previous bladder cancer that was intermediate- or high-risk** • **a disease-free interval of at least 6 months** • **solitary papillary recurrence** • **a tumour diameter of 3 mm or less.**
Relative value placed on the outcomes considered	The GDG considered recurrence, progression and treatment-related morbidity to be the most important outcomes because they reflect the benefits and harms to patients of the possible change in NHS practice. Residual tumour rate and health-related quality of life were specified as outcomes in the PICO but were not reported in the evidence. No additional outcomes to those specified in the PICO were used to make recommendations.
Quality of the evidence	The quality of the evidence was very low as assessed with GRADE. The evidence was limited because there was a lack of high quality comparative studies. The included studies had a short duration of follow-up and small sample sizes. The GDG were not confident in the patient-reported pain and treatment-related morbidity data. From clinical experience the GDG considered that the pain associated with fulguration would be greater than reported in the evidence. These issues with the evidence meant that the GDG were cautious about weighing up the benefits and harms of fulguration/biopsy. The GDG used clinical experience to make a conservative recommendation about the criteria for fulguration without biopsy. The criteria are more conservative than those reported in the evidence because the GDG could not be confident in the low quality evidence presented. These recommendations were also supported by the patient/carer representatives. The GDG could not be confident in making a recommendation regarding local anaesthetic fulguration. The evidence presented did not sufficiently answer the review question so a research recommendation was made. The GDG considered that there is variation in the current practice of fulguration, so the recommendation will promote safe patient care and reduce variation in practice until there is a stronger evidence base. The research recommendation will provide an answer to review question. Very low quality health economic evidence was presented. The evidence was not directly applicable to the UK healthcare setting. Some omissions in the report make it difficult to fully appraise quality of evidence (e.g. cost inputs that were used were not fully reported). One study interpreted economic results using an atypical approach, leading to potential misleading conclusions i.e. different conclusions might be drawn when a more conventional approach is used. The GDG acknowledged the available evidence but it did not drive the decision making due to the above issues with the identified studies. The GDG set economic data as an outcome in the research recommendation due to the poor quality of the existing economic evidence.

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Trade-off between clinical benefits and harms	The GDG considered that the recommendation will potentially prevent inappropriate fulgurations without biopsy which may lead to disease progressions being detected earlier. The recommendation may also lead to the avoidance of morbidity from biopsies (such as bladder perforation) and the inconvenience of biopsies in low-risk patients. The GDG also acknowledged a possible increase in the number of biopsies and its associated risks due to the conservative criteria for fulguration without biopsies. This may also lead to an increase in patient anxiety whilst waiting for biopsy results. The GDG considered avoiding under treatment from not performing a biopsy as a priority and acknowledged the extent and variation of current practice. Ensuring consistent best practice was considered to outweigh the relatively small harms to the patient. The GDG made a conservative recommendation regarding the criteria for fulguration without biopsy which is thought to outweigh the harms of a possible increase in biopsies. This was also supported by the patient/carer representatives.
Trade-off between net health benefits and resource use	The GDG acknowledged the available health economic evidence but it did not drive their decision making due to the limitations with the evidence discussed above. No health economic model or cost analysis was developed. However, the GDG considered the potential costs and savings of the recommendation made. The costs include potentially more biopsies, although the GDG noted that the extent of increase was unknown. There may also be increased costs from more patients having general anaesthetic. The savings include fewer complications from inappropriate biopsies. There may also be savings by potentially identifying progression early and the associated reduction of further treatment.
Other considerations	No equalities issues were identified. The GDG were unsure of the extent to change in practice that implementation of the recommendation would require.

Research recommendation	**In people with exclusively low risk bladder cancer who experience recurrence does the addition of biopsy to fulguration or laser treatment improve progression, recurrence, morbidity and quality of life?**
Why is this important	Low risk bladder cancer implies cancer at low risk of recurring within the bladder and of progressing either to more aggressive cancer or to invasive cancer. The management of recurrence of this sort of cancer has been by telescopic destruction (fulguration, resection or laser) of the recurrence, usually but not always with biopsy so that the nature of the recurrence can be confirmed and progression excluded. Biopsy generally requires cystoscopy under general or regional anaesthetic, whereas small recurrent cancers can be cleared by fulguration or laser under local anaesthesia. This may have advantages (eg, avoiding admission, reduced cost) but it risks missing progression by grade or stage. This research could provide safety evidence for the wider use of avoidance of biopsy in recurrence of previously low risk bladder cancer, resulting in savings and reduced morbidity. It would reduce variation, has no adverse equality impact and the research is achievable.

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4.2.3 Re-resection in high risk non-muscle invasive bladder cancer

People with high risk non-muscle invasive bladder cancer may have residual cancer following transurethral resection and they may actually have muscle invasive bladder cancer that was not identified at the first operation. Early repeat resection (re-resection) is used to try to ensure complete cancer clearance and improve staging. It is argued that a high quality initial resection should be sufficient and that a second procedure prolongs the pathway unnecessarily.

There is variation in practice regarding the need for re-resection and the degree of urgency with which this should be performed.

Clinical question: Does re-resection in high risk NMIBC influence outcomes?

Clinical evidence (see also full evidence review)

The evidence is summarised in table 59.

Evidence Statements

Low quality evidence (Divrik *et al.*, 2010; Kim *et al.*, 2012) suggests a benefit for repeat transurethral resection in patients with high risk non muscle invasive bladder cancer in terms of bladder cancer recurrence, disease progression and bladder cancer specific mortality.

Using event free survival rates from the no re-resection group in Divrik *et al.* (2010) trial combined with the hazard ratios reported in table 59 we could expect five year recurrence free survival rates of 63% following re-resection versus 33% without no re-resection. Estimated five-year progression-free survival would be 92% following re-resection group versus 76% without re-resection.

Low quality evidence (Divrik *et al.*, 2010) suggests re-resection is associated with minor complications in approximately 9% of cases, including prolonged bleeding, epididymitis and transient urinary retention. Such complications could be avoided in patients who do not undergo re-resection

A systematic review of observational studies (Vianello *et al.*, 2011) provided low quality evidence of upstaging and tumour persistence rates at re-resection. For patients with stage T1 tumours at initial TURB, approximately 32% were found to have persistent tumour of the same or lower stage at repeated TURB. Around 9% of patients with T1 tumours at initial TURB were upstaged at repeat TURB.

No evidence was found about the impact of re-resection on health related quality of life in this population.

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Table 59: GRADE evidence profile: Does re-resection versus no re-resection in people with high risk non-muscle invasive bladder cancer influence outcomes?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Repeated resection	No repeated resection	Relative (95% CI)	Absolute	Quality
Tumour recurrence (Divrik et al., 2010; Kim et al., 2012)											
2	randomised trials	serious[1]	none	none [2]	serious[3]	none	45/140 (32.1%)	93/148 (62.8%)	HR 0.41 (0.29 to 0.59)	5yr recurrence free survival 63% (52% to 73%) with repeated resection – versus 33% with no repeated resection4	LOW
Disease progression (Divrik et al., 2010)											
1	randomised trials	serious[1]	none	None	serious[3]	none	6/93 (6.5%)	23/98 (23.5%)	HR 0.29 (0.14 to 0.61)	5yr progression free survival 92% (85% to 96%) with repeated resection – versus 76% with no repeated resection[4]	LOW
Death from bladder cancer (Divrik et al., 2010)											
1	randomised trials	serious[1]	none	None	serious[3]	none	5/93 (5.4%)	11/98 (11.2%)	HR 0.35 (0.13 to 0.94)	Cannot calculate	LOW
Radical treatment rate (Divrik et al., 2010; Kim et al., 2012)											
2	randomised trials	serious[1]	none	none [2]	serious[3]	none	26/160 (16.3%)	36/161 (22.4%)	RR 0.73 (0.42 to 1.15)	67 fewer per 1000 (from 130 fewer to 34 more)	LOW
Process related morbidity of repeated TURB (minor complications) (Divrik et al., 2010)											
1	randomised trials	serious[1]	none	None	serious[3]	none	8/93 (8.6%)	0/98 (0%)	RR 17.9 (1.05 to 305.88)	86 more per 1000	LOW
Residual tumour rate in those with stage T1 tumours (presence of same or lower stage urothelial bladder cancer at repeated TURB)											
1[5]	observational studies	None	none	none	none	none	454/1432 (31.7%)	-	-	317 per 1000	LOW
Upstaging rate in those with stage T1 tumours (presence of higher stage urothelial bladder cancer at repeated TURB)											
1[3]	observational studies	None	none	none	none	none	74/833 (8.9%)	-	-	89 per 1000	LOW
T0 (disease free) rate at repeated TURB for those with stage T1 tumours at initial TURB											
1[5]	observational studies	none	none	none	none	none	719/1432 (50.2%)	-	-	502 per 1000	LOW
Ta rate at repeated TURB for those with stage T1 tumours at initial TURB											
1[5]	observational	none	none	none	none	none	132/1432	-	-	92 per 1000	LOW

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Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Repeated resection	No repeated resection	Relative (95% CI)	Absolute	Quality
	studies						(9.2%)				
Tis rate at repeated TURB for those with stage T1 tumours at initial TURB											
1[5]	observational studies	none	none	none	none	none	185/1432 (12.9%)	-	-	129 per 1000	LOW
Health related quality of life (including patient reported) - not measured											
0	No evidence										

[1] In Kim et al. (2012) the initial TUR differed between treatment groups. In both studies (Divrik et al. 2010, Kim et al. 2012) analysis was not by intention to treat; [2] In Kim et al. (2012) it was unclear whether all patients had high risk NMBIC - 50% had stage Ta tumours; [3] Low number of events (<300 in total); [4] Calculated using the pooled HR and the 5 year event free rates from the control arm of Divrik et al. (2010)

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**If the first TURBT shows high-risk non-muscle-invasive bladder cancer, offer another TURBT as soon as possible and no later than 6 weeks after the first resection.**
Relative value placed on the outcomes considered	Upstaging and progression were considered by the GDG to be important outcomes. Both affect outcomes for patients and may change treatment decisions, for example radical treatment might be considered in cases of upstaging. Quality of life and patient-reported outcomes were specified as outcomes in the PICO but were not reported in the evidence. Recurrence and residual tumour rate were not considered useful given the evidence on upstaging.
Quality of the evidence	The evidence was assessed as being of low quality using GRADE. There were limitations in the study by Kim et al. (2012) because immediate further resection under pathology guidance was performed rather than subsequent resection, so its relevance to the review question is limited. However, the study provides some further evidence about the importance of obtaining detrusor muscle in the biopsy specimen and the outcomes from performing a further resection. Further limitations of the evidence include a lack of intention-to-treat analysis and a low number of events in the two randomised trials. The GDG considered that the lack of intention to treat analysis was unlikely to have confounded the outcome and despite the low number of events the results were still statistically significant.
Trade-off between clinical benefits and harms	The potential benefit of the recommendation made is the more effective identification of muscle invasive disease. Performing re-resection within 6 weeks could improve outcomes for patients with high-risk non-muscle invasive bladder cancer. The potential harms arise from the psychosocial and clinical morbidity associated with the delay of definitive treatment, and the risk associated with a second resection including general anaesthetic and operative risks. The GDG considered that morbidity from resection is low and the importance of accurate staging was prioritised in the decision making.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG were unsure of costs or savings as there is uncertainty as to what extent the recommendation varies from current practice across the UK. The GDG identified that there may be costs from increased numbers of

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	resections and potential subsequent radical treatment for patients who are upstaged. There may be savings from reduced cost of assessing and treating patients with progressive or recurrent disease, some of which could be incurable, and from less cystoscopy follow-up in patients undergoing cystectomy.
Other considerations	No equalities issues were identified. The GDG were uncertain to what extent the recommendation varies from current practice across the UK. The GDG discussed the feasibility of performing re-resection in under 6 weeks. The studies presented in the evidence review typically reported a timeframe of 2-6 weeks, but there was no evidence comparing delay in re-resection. Therefore the GDG agreed to recommend the 6 week timeframe from the studies, and considered this to be feasible in current practice,

4.2.4 BCG or primary cystectomy in high risk non-muscle invasive bladder cancer

High risk non-muscle invasive bladder cancer has a high risk of progression to muscle invasive cancer and spread beyond the bladder. In order to reduce this risk, active treatments such as intravesical BCG or radical cystectomy are usually considered.

Intravesical BCG reduces the risk of cancer progression, and for people treated successfully with intravesical BCG, major surgery is avoided. However, recurrence and progression are common after intravesical BCG and often result in radical cystectomy. Intravesical BCG can delay the identification of worsening cancers and has a significant side effect profile.

Primary cystectomy is advocated as a more effective cancer treatment than intravesical BCG but if primary cystectomy is used routinely, patients who would have been cured by intravesical BCG alone will have had considerable over treatment with the consequent life changing effects and considerable risks associated with radical cystectomy.

There is wide variation in the use of both of these treatments, and whether a choice between them is offered.

Clinical question: For which patients with non-muscle invasive bladder cancer would primary cystectomy produce better outcomes than BCG?

Clinical evidence (see also full evidence review)

The clinical evidence is summarised in tables 60 to 62

Evidence statements

Radiotherapy versus observation or BCG therapy

Moderate quality evidence from one randomised trial of 204 patients (Harland et al., 2007) suggests uncertainty over whether radiotherapy is more or less effective than observation or BCG therapy in terms of recurrence-free survival, progression-free survival and overall survival. 5/102 (5%) of patients in the radiotherapy arm experienced long-term toxicity. 18% of the radiotherapy arm and 13% of the control arm underwent cystectomy due to recurrence or progression.

Primary cystectomy versus primary conservative treatment

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Very low quality evidence from two retrospective studies (336 patients) suggests uncertainty over whether primary cystectomy is more or less effective than primary conservative treatment (observation or intravesical therapy) in terms of progression or overall survival. Conservative treatment was associated with better five-year disease-specific survival than primary cystectomy in three studies of 664 patients (Badalato et al., 2012; Park et al., 2009; Patard et al., 2001). However, in one study (Park et al., 2009) patients undergoing cystectomy were older, more likely to have proper muscle absent in the TUR specimen and included a higher proportion of gross non-papillary tumours, all of which were associated with reduced disease-specific survival. Three studies reported disease-specific mortality rates in 337 patients. There were no differences in disease-specific mortality in two studies. Low quality evidence from six studies (914 patients) reported a subsequent cystectomy rate of 26% in patients initially treated by conservative therapy.

Early cystectomy versus deferred cystectomy

Very low quality evidence from one study of 77 patients suggests uncertainty about the difference in five-year overall survival between patients treated with early cystectomy compared with patients undergoing deferred cystectomy after BCG failure (72.2% versus 73.2% five-year survival, p=0.75) (Wong *et al.*, 2009). Three studies (583 patients) suggest reduced disease-specific survival in patients undergoing deferred cystectomy, with five-year disease-specific survival ranging from 78% to 84% across studies for early cystectomy and from 67% to 75% across studies for deferred cystectomy (Hautmann *et al.*, 2009; Denzinger *et al.*, 2008; Ali-el-Dein *et al.*, 2011). Ten-year disease-specific survival ranged from 69% to 79% across studies for early cystectomy and from 51% to 64% for deferred cystectomy. Denzinger et al. (2008) reported that concomitant CIS was related to a decrease in disease-specific survival in the deferred cystectomy group only. One systematic review including 3088 patients, reported that disease-specific survival after progression from high-risk NMIBC in initially conservatively treated patients was 35% after a median follow-up of 48-123 months (van den Bosch & Alfred Witjes 2011). The disease-specific mortality rate in 1136 clinical T1G3 patients who underwent radical cystectomy was 29.8% at five years (Fritsche et al., 2010). 50% of this cohort were upstaged to pT2 or higher at cystectomy.

One study of 105 patients reported that 7% of patients had major surgical complications which were distributed equally between early and deferred cystectomy groups, including two fatal pulmonary emboli and one fatal cardiac ischaemia.

One study (Kamat et al., 2006) provides very low quality evidence from 30 patients with micro-papillary bladder cancer. 12 patients undergoing cystectomy as initial therapy had ten-year disease-specific survival of 72%, whilst in 18 patients who underwent cystectomy after progression the median disease-specific survival was 61.7 months with no patient surviving ten years. Very low quality evidence from one study of 138 patients (Cheng et al., 1999) of patients with primary CIS suggests uncertainty about a difference in 15-year progression-free survival and disease-specific survival between those treated with immediate cystectomy and those that were not (some deferred cystectomy, some intravesical therapy). Radical cystectomy performed within three months after the initial diagnosis was associated with improved overall survival, but this was not significant after controlling for age.

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Table 60: GRADE evidence profile: For which patients with non-muscle-invasive bladder cancer would primary cystectomy produce better outcomes than BCG? Comparison: Radiotherapy versus control (observation or intravesical therapy) for T1G3 bladder cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	Control	Relative (95% CI)	Absolute	Quality
Progression (time to detection of pT2 tumour or higher, cystectomy, metastases or treatment; follow-up median 44 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	32/102 (31.4%) Median interval not met	33/102 (32.4%) Median interval not met	HR 1.07 (0.65 to 1.74)	5-year progression-free interval 62% versus 63%	MODERATE
Progression (as above but death from any cause included as event; follow-up median 44 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	57/102 (55.9%) Median 49 months	49/102 (48%) Median 66 months	HR 1.35 (0.92 to 1.98)	5-year progression-free survival 41% versus 52%	MODERATE
Death from any cause (follow-up median 44 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	45/102 (44.1%) Median 67 months	39/102 (38.2%) Median 88.5 months	HR 1.32 (0.86 to 2.04)	5-year overall survival 52.5% versus 61%	MODERATE
Recurrence (time to recurrence of a bladder tumour (invasive or otherwise), cystectomy, metastases or treatment or disease-related death; follow-up median 44 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	61/102 (59.8%) Median 16 months	66/102 (64.7%) Median 12.5 months	HR 0.77 (0.54 to 1.10)	5-year recurrence-free interval 40% versus 30.5%	MODERATE
Recurrence (as above but death from any cause included as an event; follow-up median 44 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	78/102 (76.5%) Median 13 months	71/102 (69.6%) Median 12 months	HR 0.94 (0.67 to 1.30)	5-year recurrence-free survival 31% versus 29%	MODERATE
Long-term toxicity (assessed 12 months or more after study entry)											

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
1[1]	randomised trials	none	none	none	serious[2]	none	5/102 (4.9%)	0/102 (0%)	-	-	MODERATE
Cystectomy rate											
1[1]	randomised trials	none	none	none	serious[2]	none	18/102 (17.6%)	13/102 (12.7%)	RR 1.38 (0.72 to 2.67)	48 more per 1000 (from 36 fewer to 213 more)	MODERATE
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Harland et al. 2007; [2] Low number of events / confidence interval includes value of no effect

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Table 61: GRADE evidence profile: For which patients with non-muscle-invasive bladder cancer would primary cystectomy produce better outcomes than BCG? Comparison: Primary cystectomy versus conservative treatment (surveillance or intravesical therapy) for high-risk non muscle invasive bladder cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Primary RC	Conservative treatment	Relative (95% CI)	Absolute	Quality
Progression (median follow-up 6.9 – 8.3 years; assessed with: Number of patients progressing over follow-up)											
2[1]	observational studies	none	none	none	serious[2]	none	27/101 (26.7%)	55/172 (32%)	RR 0.86 (0.58 to 1.27)	45 fewer per 1000 (from 134 fewer to 86 more)	VERY LOW
Overall mortality (median follow-up 6.9 – 8.3 years; assessed with: 10-yr overall mortality rate)											
2[1]	observational studies	none	none	none	serious[2]	none	71/164 (43.3%)	75/172 (43.6%)	RR 1.00 (0.78 to 1.28)	0 fewer per 1000 (from 96 fewer to 122 more)	VERY LOW
Overall mortality (median follow-up 4.3 – 6.9 years assessed with: 5-yr overall mortality rate)											
2[3]	observational studies	none	none	none	serious[2]	none	31/113 (27.4%)	82/425 (19.3%)	RR 1.38 (0.97 to 1.95)	73 more per 1000 (from 6 fewer to 183 more)	VERY LOW
Disease-specific mortality (median follow-up 62 mo – 8.3 years assessed with: mortality rate due to bladder cancer)											
3[4]	observational studies	none	none	none	serious[2]	none	29/115 (25.2%)	46/222 (20.7%)	RR 1.22 (0.81 to 1.84)	-	VERY LOW
Disease-specific survival at 5 years											
3[5]	observational studies	serious[6]	none	none	serious[2]	none	64% to 84%	80% to 96%	n/a	All 3 studies favour conservative treatment for 5yr DSS rates	VERY LOW
Cystectomy rate											
6[7]	observational studies	none	none	none	none	none	-	238/914 (26%)8	-	-	LOW
Treatment-related mortality											

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Primary RC**	**Conservative treatment**	**Relative (95% CI)**	**Absolute**	**Quality**
0	No evidence										
Treatment-related morbidity											
0	No evidence										
Health-related quality of life											
0	No evidence										

[1] De Berardinis et al. 2011, Thalman et al. 2004; [2] Low number of events / confidence interval includes value of no effect; [3] Thalman et al. 2004, Dalbagni et al. 2009; [4] De Berardinis et al. 2011, Thalman et al. 2004, Patard et al. 2001; [5] Badalato et al. 2012, Park et al. 2009, Thalman et al. 2004; [6] In Park et al. (2009) patients undergoing RC were older, more likely to have proper muscle absent in the TUR specimen and a higher proportion of gross non-papillary tumours, all of which were factors associated with reduced disease-specific survival. Inclusion of this study increases the effect size and confidence interval in favour of conservative treatment; [7] De Berardinis et al. 2011, Thalman et al. 2004, Patard et al. 2001, Badalato et al. 2012, Dalbagni et al.2009, Iida 2009; [8] None of the studies reported a significant difference in survival between primary RC and delayed RC

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Table 62: GRADE evidence profile: For which patients with non-muscle-invasive bladder cancer would primary cystectomy produce better outcomes than BCG? Comparison: Early cystectomy versus deferred cystectomy for high-risk non-muscle invasive bladder cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Primary RC	Deferred RC	Relative (95% CI)	Absolute	Quality
Metastases-free survival											
0	No evidence available										
Overall mortality (follow-up median 53 months; assessed with: 5-yr mortality rate)											
1[1]	observational studies	none	none	none	serious[2]	none	10/36 (27.8%)	11/41 (26.8%)	RR 1.04 (0.50 to 2.15)	11 more per 1000 (from 134 fewer to 309 more)	VERY LOW
Disease-specific mortality (follow-up median 58 mo to 5.4 yrs; assessed with: 5-yr mortality rate)											
3[3]	observational studies	none	none	none	serious[2]	none	67/363 (18.5%)	62/220 (28.2%)	RR 0.65 (0.48 to 0.89)	99 fewer per 1000 (from 31 fewer to 147 fewer)	VERY LOW
Disease-specific mortality (follow-up median 58 mo to 5.4 yrs; assessed with: 10-yr mortality rate)											
3[3]	observational studies	none	none	none	serious[2]	none	91/363 (25.1%)	85/220 (38.6%)	RR 0.65 (0.51 to 0.84)	135 fewer per 1000 (from 62 fewer to 189 fewer)	VERY LOW
Disease-specific mortality (Micropapillary tumours) (follow-up 1.7-181.2 months)											
1[4]	observational studies	none	none	none	serious[5]	none	2/12 (16.7%)	8/18 (44.4%)	RR 0.38 (0.10 to 1.47)	276 fewer per 1000 (from 400 fewer to 209 more)	VERY LOW
Disease-specific mortality (CIS only) (follow-up mean 11 years)											
1[6]	observational studies	none	none	serious[7]	serious[5]	none	10/43 (23.3%)	27/95 (28.4%)	RR 0.82 (0.44 to 1.54)	51 fewer per 1000 (from 159 fewer to 153 more)	VERY LOW
Overall mortality (CIS only) (follow-up mean 11 years)											
1[6]	observational studies	none	none	serious[7]	serious[5]	none	17/43 (39.5%)	66/95 (69.5%)	RR 0.57 (0.38 to 0.84)	299 fewer per 1000 (from 111 fewer to 431 fewer)	VERY LOW
Treatment-related mortality											
1[8]	observational studies	none	none	None	serious[9]	none	3/105 (2.9%)10		-	-	VERY LOW
Treatment-related morbidity (assessed with: impaired wound healing)											

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Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Primary RC**	**Deferred RC**	**Relative (95% CI)**	**Absolute**	
1[8]	observational studies	none	none	none	serious[9]	none	4/105 (3.8%)		-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Wong et al. 2009 (abstract only); [2] Small sample size / low number of events;[3] Hautmann et al. 2009, Denzinger et al. 2008, Ali-el-Dein et al. 2011, [4] Kamat et al. 2006; [5] Low number of events / confidence interval includes null value; [6] Cheng et al. 1999; [7] Control group includes patients who underwent deferred RC and those treated with intravesical therapy or radiotherapy only; [8] Denzinger et al. 2008; [9] Low number of events - events not reported separately for early and deferred RC; [10] 2 fatal pulmonary embolia, 1 fatal cardiac ischaemia

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Cost-effectiveness evidence

The primary results of the analysis by Kulkarni et al. 2009 are summarised in table 63.

The base case results of the cost-effectiveness analysis showed that immediate cystectomy was cheaper and more effective than conservative therapy (BCG with possible delayed cystectomy) i.e. immediate cystectomy was found to be the dominant strategy.

Scenario analyses, in which age and co-morbid status were varied, showed that the optimal strategy is likely to be different for different patient subgroups. The analysis showed that immediate cystectomy was dominant in patients aged ≤55 years old regardless of co-morbid status. For patients ≥70 years old, conservative therapy was either dominant or had an ICER that was likely to be considered cost-effective (≤$32,700 per QALY). For patients between ages 60 and 70 years old, the optimal choice was dependent upon co-morbidities, with increased co-morbid burden making conservative therapy more cost-effective.

The probabilistic sensitivity analyses (PSA) showed that immediate cystectomy was found to be cost-effective in 70% and 67% of simulations at thresholds of $20,000 and $50,000 per QALY, respectively.

The results suggest that, compared with a conservative strategy using BCG, immediate radical cystectomy yielded better outcomes and lower costs for the *average* patient. Furthermore, the results suggest that tailoring therapy based on patient age and co-morbidity may increase survival and yield significant costs savings for the health care system.

However, there are reservations about the applicability of the analysis because it considered the Canadian health care system which may not reflect the UK setting. There were also concerns about the quality of life data that were used as they were not all patient reported and were often not drawn from patients with bladder cancer (data from prostate, lung and breast cancer were used). Potentially serious limitations were also identified as, although a systematic literature review was conducted, some of the evidence informing the model was not considered to be of high quality. Furthermore, costs were not always sourced from patients with bladder cancer, such as chemotherapy costs, which were based on patients with non-small cell lung cancer.

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Table 63: Modified GRADE table showing the included evidence for treatments for high risk non-muscle invasive bladder cancer

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Kulkarni et al. 2009	Men with incident, high-risk, T1G3 bladder cancer.	"BCG" - Initial conservative therapy, which consisted of intravesical BCG with possible delayed cystectomy	$42,600	10.60 LYs 9.39 QALYs	Reference			Scenario analyses Several scenario analyses were conducted in which age and co-morbid status was varied. The results showed that regardless of co-morbid status, immediate cystectomy ws found to be the dominant strategy in patients aged ≤55 years old. At ≥70 years, conservative therapy was either dominant or had an ICER that was likely to be considered cost-effective (≤$32,700 per QALY). Between ages 60 and 70 years, the optimal choice was dependent upon co-morbidities, with increased co-morbid burden making conservative therapy more cost-effective. Probabilistic	Partially applicable Not a UK study (Canadian), thus estimated costs and benefits might not apply to UK health care setting. Quality of life values were not all patient reported and were often not drawn from patients with bladder cancer (data from prostate, lung and breast cancer patients was used). Potentially serious limitations Although systematic literature review was conducted, evidence identified and utilised was not always of high quality. Costs were not always sourced from patients with bladder cancer. For instance chemotherapy costs were based on patients with non-small
		"Cystectomy" - immediate nerve sparing radical cystectomy with an orthotopic ileal neobladder	$37,600	11.01 LYs 9.46 QALYs	-$5,000	0.41 LYs 0.07 QALYs	Cystectomy is dominant using both effectiveness measures		

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
								sensitivity analyses (PSA) PSA was conducted using 1000 2nd order Monte Carlo simulations. The immediate cystectomy strategy was found to be cost-effective in 70% and 67% of simulations at thresholds of $20,000 and $50,000 per QALY, respectively.	cell lung cancer While PSA and scenario analyses were performed, further sensitivity analysis could have been conducted to better explore uncertainty.
	Comments:								

Recommendations	**Offer the choice of intravesical BCG (Bacille Calmette-Guérin) or radical cystectomy to people with high-risk non-muscle-invasive bladder cancer, and base the choice on a full discussion with the person, the clinical nurse specialist and a urologist who performs both intravesical BCG and radical cystectomy. Include in your discussion:** • **the type, stage and grade of the cancer, the presence of carcinoma in situ, the presence of variant pathology, prostatic urethral or bladder neck status and the number of tumours** • **risk of progression to muscle invasion, metastases and death** • **risk of understaging** • **benefits of both treatments, including survival rates and the likelihood of further treatment** • **risks of both treatments** • **factors that affect outcomes (for example, comorbidities and life expectancy)** • **impact on quality of life, body image, and sexual and urinary function.**
Relative value placed on the outcomes considered	The outcomes of progression, survival, recurrence, cystectomy rate, and health-related quality of life were considered to be the most important. These are the main disease-specific outcomes for high risk non-muscle invasive bladder cancer. The evidence review suggested that these informed the natural history of the disease following treatment by BCG, radical radiotherapy and cystectomy. No evidence was identified for health-related quality of life.
Quality of the evidence	The quality of the evidence was assessed with GRADE as being very low to moderate. The best evidence available was a randomised trial comparing radical radiotherapy with BCG. Limitations of the evidence were that most studies were retrospective and therefore had a risk of selection bias. There were inconsistencies in the terminology used for delayed and deferred cystectomy. These issues made the evidence unreliable regarding the decision on which patients should receive BCG or cystectomy and the GDG considered this when reaching consensus. The recommendation for discussion of treatment options with health care professionals was based on clinical consensus. There was no evidence on this issue but it was considered critical to enable the patient to take an informed decision if they chose to. This is considered to be consistent with best practice. The GDG made a recommendation because patients with non-muscle invasive bladder cancer need to be treated. However, it was unclear from the available evidence which is the most effective primary treatment option. It was therefore agreed that further research into this area is needed. A research recommendation was made because of the lack of good quality evidence about which intervention is more clinically effective and cost effective. The research recommendation will also provide much

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	needed evidence about the specific impact of these treatments on quality of life outcomes. Low quality economic evidence was identified from one Canadian study. This evidence was limited because the economic analysis was performed using Canadian costs, which may not be directly comparable with UK costs. Also, quality of life was estimated by clinicians rather than patients and the clinical effectiveness data informing the model differed from the clinical evidence review. The study also reported poorly defined clinical utility measures without reference to the information sources. These limitations meant that the GDG were unable to rely on the model to inform the recommendations. The GDG reached consensus assuming equipoise of treatments.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of the recommendation is that patients with high risk non-muscle invasive bladder cancer should have a better informed and balanced discussion regarding their treatment. This should improve their understanding of the disease and should improve clinical outcomes. The GDG considered that there is a potential for an increase in cystectomies with the possible risk of over-treatment for some patients. Also, the discussion about treatment options could result in an overload of information for some patients, especially those who would prefer to delegate decision making. The GDG balanced the benefits against the harms by considering that patients must be given the opportunity to access full information about their prognosis and the potential benefits and risks of treatment, including the impact on quality of life. The GDG considered that giving this opportunity to all patients was of greater benefit than of giving too much information to some patients. Information and support in decision making is important for patients to make an informed decision regarding treatment, taking into account their preferences as well as prognostic information.
Trade-off between net health benefits and resource use	Low quality health economic evidence was identified from one Canadian study. However, the GDG were unable to rely on the evidence to inform the recommendations because of the limitations discussed above. The GDG reached consensus assuming equipoise of treatments. No health economic model was developed for this topic. The GDG considered that there are potential changes for working within clinical networks and some more review of patients necessary by specialist teams, which could incur extra costs to the NHS. The GDG agreed that there could be savings from reduced treatment of advanced disease due to an improved cure rate.
Other considerations	No equalities issues were identified. The GDG considered that the recommendations may alter practice in the areas served by some former cancer networks, with an increase in referral of patients to central services. The GDG considered that the evidence for BCG from section 4.2.1 would be relevant to this area. The recommendation for patients to be reviewed by a specialist performing BCG/Cystectomy was made with knowledge of current thinking of best practice. Involvement of the CNS

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	is consistent with the NICE Urological Cancers Improving Outcomes Guidance.

Research recommendation	**Is primary radical cystectomy more effective than primary intravesical BCG in high-risk non-muscle-invasive bladder cancer, in terms of quality of life and cancer-specific outcomes?**
Why is this important	Options for people with high-risk non-muscle-invasive bladder cancer include cystoscopy surveillance, BCG immunotherapy or radical surgery. To date, these have not been directly compared across the same population to understand their relative benefits. Bladder-sparing approaches avoid major surgery, but have a greater risk of cancer progression. The potential advantage of bladder-sparing approaches compared with cystectomy in maintaining quality of life may be offset by continuing concern about cancer progression and morbidity from treatment. Primary cystectomy may improve survival; however, it has high short term risks and life changing consequences. It will be overtreatment for those people whose cancer would not have progressed.

4.2.5 Treatment following failure of BCG

Failure to respond to intravesical BCG includes cancer still present after induction BCG or recurrent cancer during or after maintenance BCG treatment. Residual or recurrent cancer may be non muscle invasive or muscle invasive. Intravesical BCG failure can also include patients who did not complete their treatment due to intravesical BCG related side effects (called BCG intolerant), and therefore they may or may not be clear of cancer.

This section focuses on people with residual or recurrent non-muscle invasive bladder cancer following intravesical BCG and people who have not tolerated intravesical BCG.

The treatment options for these patients include radical cystectomy or some form of bladder sparing treatment. Radical cystectomy has the highest cure rate but may be over treatment and has life changing effects and considerable risks. The bladder sparing treatments include further intravesical BCG, intravesical chemotherapy or radical radiotherapy. These approaches avoid removal of the bladder, but carry the risk that the tumour may not respond and will progress to invasion or spread beyond the bladder. They also have side effects.

There is currently considerable variation in the management of people with non-muscle invasive bladder cancer who have failed intravesical BCG therapy.

Clinical question: What is the optimum treatment for patients with non-muscle invasive bladder cancer who have failed BCG?

Clinical evidence (see also full evidence review)

The evidence is summarised in tables 64 to 67

Evidence statements

Gemcitabine versus Mitomycin C

Moderate quality evidence from one randomised trial (Addeo et al., 2009) of 109 patients suggests uncertainty over the incidence of tumour recurrence in gemcitabine- versus mitomycin C-treated patients. Although incidence of tumour recurrence was lower in gemcitabine treated patients after 36 months of follow up, the 95% confidence interval around the estimated effect included both no effect and considerable benefit for gemcitabine.

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Moderate quality evidence from one randomised trial of 109 patients (Addeo et al., 2010) suggests uncertainty over the incidence of tumour progression in gemcitabine- versus mitomycin C-treated patients. Incidence of tumour progression was lower in gemcitabine treated patients after 36 months of follow up, but the 95% confidence interval around the estimated effect was wide and included considerable harm, no effect and considerable benefit for gemcitabine.

Moderate quality evidence from one randomised trial of 109 patients (Addeo et al., 2010) suggested that gemcitabine treatment was associated with fewer adverse events than mitomycin C.

Gemcitabine versus intravesical BCG

Two studies (Di Lorenzo et al., 2010; Gacci et al., 2006) compared the effectiveness of gemcitabine to BCG. Meta-analysis of the results was not possible due to differences in study design and outcome definitions.

Moderate quality evidence from one randomised trial of 80 patients (Di Lorenzo et al., 2010) suggests that the incidence of tumour recurrence after 12 months is lower in patients treated with gemcitabine compared to treatment with BCG. In patients experiencing recurrence (n=56), there was no significant difference between treatment groups in the incidence of cystectomy due to disease progression. The incidence of grade two and grade three adverse events was similar for both treatments.

Very low quality evidence from one observational trial of 19 patients (Gacci et al., 2006) found no significant difference in tumour recurrence, overall survival, bladder preservation rates or adverse events between gemcitabine and BCG treatment.

BCG versus chemotherapy (MMC or epirubicin)

Very low quality evidence from one observational trial of 183 patients (Matsumoto et al., 2012) suggests that rates of recurrence-free survival (after five years of follow up) are greater in patients treated with BCG than in patients treated with chemotherapy (MMC or epirubicin).

BCG versus BCG plus interferon α2B

Very low quality evidence from one observational trial of 139 patients (Prasad et al., 2009) suggests that the incidence of disease recurrence is lower in patients treated with BCG alone compared with BCG in combination with interferon α2B.

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Table 64: GRADE evidence profile: What is the optimum treatment for patients with non-muscle-invasive bladder cancer who have failed BCG? Comparison: mitomycin C compared to gemcitabine

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mitomycin C	Gemcitabine	Relative (95% CI)	Absolute	Quality
Incidence of recurrence (follow-up median 36 months; assessed with positive cytoscopy)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	none	22/55 (40%)	15/54 (27.8%)	RR 1.44 (0.84 to 2.47)	122 more per 1000 (from 44 fewer to 408 more)	MODERATE
Number of patients with tumour progression (follow-up median 36 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	10/55 (18.2%)	6/54 (11.1%)	RR 1.64 (0.64 to 4.19)	71 more per 1000 (from 40 fewer to 354 more)	MODERATE
Number of patients developing metastases (median follow-up 36 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	1/55 (1.8%)	1/54 (1.9%)	RR 0.98 (0.06 to 15.3)	0 fewer per 1000 (from 17 fewer to 265 more)	LOW
Overall survival											
0	No evidence						-	-	-	-	
Bladder preservation rates											
0	No evidence						-	-	-	-	
Incidence of adverse events (follow-up median 36 months)4											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40/55 (72.7%)	21/54 (38.9%)	RR 1.87 (1.29 to 2.71)	338 more per 1000 (from 113 more to 665 more)	MODERATE
Treatment related mortality											
0	No evidence						-	-	-	-	
Treatment related morbidity											
0	No evidence						-	-	-	-	
Health related quality of life											
0	No evidence						-	-	-	-	

[1] Total number of events is less than 300. [2].95% confidence interval around the relative effect includes both no effect and appreciable benefit. [3] 95% confidence interval around the relative effect includes no effect, appreciable benefit and appreciable harm. [4] Proportion of adverse events deemed related to treatment was not reported.

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Table 65: GRADE evidence profile: What is the optimum treatment for patients with non-muscle-invasive bladder cancer who have failed BCG? Comparison: gemcitabine compared to BCG

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine	BCG	Relative (95% CI)	Absolute	Quality
Overall mortality (follow-up median 15 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	0/40 (0%)	1/40 (2.5%)	RR 0.33 (0.01 to 7.95)	17 fewer per 1000 (from 25 fewer to 174 more)	LOW
Incidence of tumour recurrence (follow-up 12 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21/40 (52.5%)	35/40 (87.5%)	RR 0.6 (0.44 to 0.82)	350 fewer per 1000 (from 157 fewer to 490 fewer)	MODERATE
Time to first recurrence (median follow-up 15 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	21/40 (52.5%)	35/40 (87.5%)	HR 1.1 (0.8 to 1.2)	3.9 months (GEM group) vs 3.1 months (BCG group)	MODERATE
Incidence of cystectomy due to disease progression in patients with recurrent disease											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,3]	none	7/21 (33.3%)	13/35 (37.1%)	RR 0.9 (0.43 to 1.89)	37 fewer per 1000 (from 212 fewer to 331 more)	MODERATE
Incidence of grade 2 adverse events											
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,3]	none	12/40 (30%)	13/40 (32.5%)	RR 0.92 (0.48 to 1.77)	26 fewer per 1000 (from 169 fewer to 250 more)	MODERATE
Incidence of grade 3 adverse events											
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	3/40 (7.5%)	3/40 (7.5%)	RR 1 (0.21 to 4.66)	0 fewer per 1000 (from 59 fewer to 275 more)	LOW
Overall mortality (follow-up median 15 months)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	0/9 (0%)	2/10 (20%)	RR 0.22 (0.01 to 4.05)	156 fewer per 1000 (from 198 fewer to 610 more)	VERY LOW
Incidence of tumour recurrence (follow-up 12 months)											
1	observational studies	no serious	no serious inconsistency	no serious indirectness	serious[1]	none	6/9 (66.7%)	5/10 (50%)	RR 1.33 (0.62 to	165 more per 1000 (from 190	VERY LOW

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Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gemcitabine**	**BCG**	**Relative (95% CI)**	**Absolute**	
		risk of bias							2.89)	fewer to 945 more)	
Bladder preservation rate											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,3]	none	7/9 (77.8%)	6/10 (60%)	RR 1.30 (0.7 to 2.4)	180 more per 1000 (from 180 fewer to 840 more)	VERY LOW
Incidence of adverse events											
1[4]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	2/9 (22.2%)	3/10 (30%)	RR 0.74 (0.16 to 3.48)	78 fewer per 1000 (from 252 fewer to 744 more)	VERY LOW
Metastasis free survival											
0	No evidence						-	-	-	-	
Treatment related mortality											
0	No evidence						-	-	-	-	
Treatment related morbidity											
0	No evidence						-	-	-	-	
Health related quality of life											
0	No evidence						-	-	-	-	

[1] Total number of events was less than 300. [2] Total population size was less than 400. [3] 95% confidence interval around the relative effect includes appreciable harm, no effect and appreciable benefit [4] Proportion of adverse events deemed related to treatment was not reported.

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Table 66: GRADE evidence profile: What is the optimum treatment for patients with non-muscle-invasive bladder cancer who have failed BCG? Comparison: BCG compared to chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BCG**	**Chemotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**
Recurrence free survival (median follow-up 5.1 years)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/119 (59.7%)	5/24 (20.8%)	RR 2.89 (1.29 to 6.33)-	208 fewer per 1000 (from 208 fewer to 208 fewer)	VERY LOW
Overall survival											
0	No evidence						-	-	-	-	
Disease specific survival											
0	No evidence						-	-	-	-	
Metastasis free survival											
0	No evidence						-	-	-	-	
Bladder preservation rates											
0	No evidence						-	-	-	-	
Treatment related mortality											
0	No evidence						-	-	-	-	
Treatment related morbidity											
0	No evidence						-	-	-	-	
Health-related quality of life											
0	No evidence						-	-	-	-	

[1] Patients' treatment was based on clinician preference. Higher risk patients may have been disproportionately assigned to BCG treatment. [2] Total number of events was less than 300.

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Table 67: GRADE evidence profile: What is the optimum treatment for patients with non-muscle-invasive bladder cancer who have failed BCG? Comparison: BCG alone compared to BCG plus interferon α2B

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG	BCG + IFN α2B	Relative (95% CI)	Absolute	Quality
Disease recurrence (median follow-up 55.6 months)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	65/114 (57%)	21/25 (84%)	RR 0.68 (0.54 to 0.86)	269 fewer per 1000 (from 118 fewer to 386 fewer)	VERY LOW
Overall survival											
0	No evidence						-	-	-	-	
Disease specific survival											
0	No evidence						-	-	-	-	
Metastasis free survival											
0	No evidence						-	-	-	-	
Bladder preservation rates											
0	No evidence						-	-	-	-	
Treatment related mortality											
0	No evidence						-	-	-	-	
Treatment related morbidity											
0	No evidence						-	-	-	-	
Health related quality of life											
0	No evidence						-	-	-	-	

[1] *Total number of events was less than 300.*

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**If induction BCG fails (because it is not tolerated, or bladder cancer persists or recurs after treatment with BCG), refer the person's care to a specialist urology multidisciplinary team.** **For people in whom induction BCG has failed, the specialist urology multidisciplinary team should assess the suitability of radical cystectomy, or further intravesical therapy if radical cystectomy is unsuitable or declined by the person, or if the bladder cancer that recurs is intermediate- or low-risk.**
Relative value placed on the outcomes considered	The GDG prioritised the cancer-related outcomes of recurrence, progression, survival and treatment-related morbidity, as these are of the greatest importance to patients. Progression in particular leads to further treatment and is associated with worse prognosis. The GDG considered the outcome of bladder preservation rate to not be useful once the evidence had been appraised because evidence was only available for one possible comparison of treatments. This evidence was either of very low quality or reported only for a small number of patients. Quality of life was specified as an outcome in the PICO but was not reported in the evidence. No additional outcomes to those specified in the PICO were used to make recommendations.
Quality of the evidence	The quality of the evidence was very low to moderate as assessed with GRADE. The GDG considered potential issues with the evidence presented. Most notably, the lack of any systematic reviews and the unsuitability of any existing randomised trial evidence for meta-analysis. These issues meant that the GDG discussed the evidence in light of clinical experience and comments from patient representatives. The GDG considered that no specific intravesical therapies could be recommended due to the low quality and general lack of evidence. The GDG made the recommendation to refer patients to a SMDT for consideration of treatment options based on their clinical experience because there was no strong evidence in this area. The recommendation to consider cystectomy was prioritised based on clinical judgement and evidence of its effectiveness as a primary therapy in patients with high-risk NMIBC (presented in section 4.3.1). The GDG also made a research recommendation because of the uncertainty about which treatment is best for patients who fail BCG and who are also unsuitable for cystectomy. This research recommendation will help reduce the uncertainty about the effectiveness of radiotherapy and other novel intravesical therapies for these patients.

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Trade-off between clinical benefits and harms	The GDG considered the potential benefits of the recommendation. Referral to a SMDT will ensure specialist consideration of patients with high-risk NMIBC who fail BCG treatment. This includes the consideration of appropriate treatment options, such as cystectomy or further intravesical therapy. This may also prevent under-treatment of patients in this group. The GDG considered that the recommendations will enhance patient choice and informed decision-making. The GDG noted that a possible harm of the recommendation is that potentially more patients will undergo surgery, which has associated risks and morbidity. The GDG considered that the increased probability of survival and more informed decision-making for patients would outweigh the potential increase in morbidity from surgery.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG considered that the potential costs of the recommendations made include increased workload for SMDTs and that potentially a greater number of patients will undergo surgery. The GDG considered that if potentially more patients undergo surgery as a result of the recommendations, then savings will be made from less intravesical therapy being administered and reduced cystoscopic follow-up. There will also be savings from reduced need for treatment of disease progression.
Other considerations	The GDG considered that cystectomy may not be an option for patients with poor manual dexterity, visual impairment or diminished mental capacity. However, the recommendations main aim is to promote equal access for all patients to specialist care. The GDG considered that the recommendations reflect best current UK practice, but acknowledged that there may be variability in adherence to this at present. The GDG therefore considered that moderate changes in practice may be required. The GDG discussed the option of radiotherapy as a treatment for this patient group. There was insufficient evidence to make a recommendation, but the GDG considered that radiotherapy could be an appropriate treatment option in a very small number of patients. The recommendation does not preclude the use of radiotherapy and a relevant research recommendation has been made. The GDG took account of the existing NICE IPG covering device-assisted Mitomycin C and a relevant recently completed but currently unpublished trial, the results of which are awaited.

Research recommendation	**In people who cannot tolerate BCG or with persistent or recurrent disease after BCG, or who are not suitable for radical cystectomy is novel intravesical therapy or radiotherapy more effective than the current standard of care (for example intravesical mitomycin-C) in terms of recurrence, progression, survival and quality of life?**
Why is this important	People with high risk non-muscle invasive bladder cancer are usually offered either instillation of BCG vaccine into their bladder or surgery to remove their bladder (cystectomy), because of the high risks that the cancer may worsen and spread into the muscle wall of the bladder. If

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Research recommendation	**In people who cannot tolerate BCG or with persistent or recurrent disease after BCG, or who are not suitable for radical cystectomy is novel intravesical therapy or radiotherapy more effective than the current standard of care (for example intravesical mitomycin-C) in terms of recurrence, progression, survival and quality of life?**
	BCG cannot be tolerated due to side effects, or if it fails to clear the cancer, people who are not fit enough for cystectomy, or who decline it, are at very high risk of progression of their cancer, and death. At present, further BCG or instillation of Mitomycin C are the other main treatment options. This research would establish the efficacy and risks of radiotherapy and of novel intravesical therapy in this group who have no effective standard treatment option at present. There would be no equality consequence, and the logistics of the research would be deliverable.

4.3 Managing side effects of treatment for non-muscle-invasive bladder cancer

Radical radiotherapy and intravesical BCG (BCG vaccine inserted into the bladder), treatments used for high risk bladder cancer that is confined to the bladder can result in patients being cured of their cancer and with their bladder preserved but with significant side effects which can result in patients having a poor quality of life.

Most people treated with intravesical BCG experience urinary frequency and urgency, visible haematuria and some pain when passing urine for 7- 10 days after each treatment. People treated with radical radiotherapy often experience similar symptoms but of lesser degree and shorter duration. However for some people these side effects continue long term.

People who experience these symptoms are usually offered simple conservative treatments, typically medication, and this is often helpful. However, as with all medication patients may experience side effects. No specific treatment has been developed for the symptoms in relation either to intravesical BCG treatment or to radical radiotherapy.

These side effects can be of a persistence and severity that interventions such as urinary catheters or occasionally even radical cystectomy may be considered. Most haematuria following intravesical BCG or radical radiotherapy will stop without any need for treatment. Treatment for persistant bleeding includes cystoscopy and diathermy, instillation of formalin or alum into the bladder. Whilst these treatments may reduce or resolve bleeding, formalin and alum can both have severe side effects. Severe bleeding can also be treated by embolisation, but this is not widely available.

Medication has been given to try to prevent or alleviate side effects in people being treated with intravesical BCG but these are not widely used. Some people are unable to complete the scheduled maintenance course of intravesical BCG because of bladder side effects and intravesical BCG schedules have been changed to improve compliance. Intravesical BCG dosage has been reduced and interval between treatments has been extended.

There is variation in the treatments that are currently offered to people who may experience or who have side effects following intravesical BCG and radical radiotherapy. Side effects are managed by a variety of different healthcare professionals in a variety of different settings.

Clinical question: What is the most effective intervention for bladder toxicity following radiotherapy or BCG therapy for bladder cancer?

Clinical evidence (see also full evidence review)

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The evidence is summarised in tables 68 to 74. No evidence was identified for health-related quality of life across any of the interventions. No evidence was identified for the following interventions specified in the PICO: cystectomy, botox, alum, embolisation, catheterisation, increased time between treatments of BCG, elmiron.

Evidence Statements

Ofloxacin

One randomised trial (115 participants) of moderate quality was identified comparing BCG therapy plus ofloxacin with BCG therapy plus placebo in patients with superficial bladder cancer. Treatment with 2 x 200mg ofloxacin with each BCG instillation resulted in a lower rate of mild to moderate adverse events compared to placebo between instillations four and six, and a lower rate of severe adverse events between instillations one and nine. However, the proportion of participants specifically with bladder toxicity was not reported, as the outcome of adverse events included both local and systemic symptoms.

Isoniazid

Two randomised trials (997 participants) provided moderate quality evidence on the efficacy of isoniazid for the prevention of BCG-induced bladder toxicity. In both studies the 95% confidence intervals of the effect sizes (risk ratios) included the null value, so there is no strong evidence that isoniazid has an effect on the rate of chemical cystitis, frequency or haematuria (van der Meijden *et al.*, 2001) or bladder toxicity (including haematuria, dysuria, and frequency) (Al Khalifa *et al.*, 2000). When toxicity was sub-grouped by severity, participants receiving isoniazid were more likely to experience mild toxicity and less likely to experience severe toxicity than the placebo group. However, it should be noted that these data were from a low number of participants.

Oxybutynin

One randomised trial (Johnson *et al.*, 2013) of 50 participants provided low quality evidence of an increase in urinary symptoms (frequency and burning) and systemic symptoms (fever, dry mouth) in those treated with oxybutynin alongside BCG treatment compared to those in the placebo group.

Reduced BCG dose

High quality evidence from one trial (663 patients) of reduced dose BCG reported by Brausi *et al.* (2014) stated that there were no differences between rates of local and systemic BCG side effects between the 1/3 dose BCG group and the full-dose BCG group (RR 0.95, 95% CI 0.86 to 1.06). Reducing the dose of BCG did not decrease the percentage of patients who discontinued treatment due to side effects.

Formalin

Two case series studies (12 participants) reported the effects of intravesical formalin for treating bladder haemorrhage secondary to radiation-induced cystitis. Both studies reported that all patients had a good response to treatment with cessation of bleeding observed for three to five months (very low quality evidence).

Hyperbaric oxygen therapy (HBOT)

Seven case series studies (153 participants) provided very low quality evidence on the efficacy of HBOT for treating radiation-induced cystitis. Overall 94/153 (61%) participants showed a complete resolution of haematuria, with effectiveness ranging from 27% to 100% across studies. In most studies patients had received previous treatment for cystitis, such as alum or formalin, without success.

Sodium hyaluronate

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One case series (54 patients) provided very low quality evidence on the efficacy of intravesical sodium hyaluronate for the treatment of chemical-induced cystitis in bladder cancer patients treated with Mitomycin C or BCG therapy. It is not stated whether Cystistat was the treatment used. Bladder capacity increased in all patients after treatment (mean difference 226.1 ml, 95% CI 207.1 to 245 ml). Patient-reported pain as measured by the Visual Analogue Scale (VAS) decreased in all patients (mean difference -7.7, 95% CI -8.12 to -7.31). VAS scores range from 1 to 10, with 10 indicating maximum pain tolerated.

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Table 68: GRADE evidence profile: The effectiveness of Ofloxacin for the prevention of BCG-induced toxicity in superficial bladder cancer

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ofloxacin**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Toxicity: At least one Class I or II adverse event (follow-up between instillations 4 and 6; assessed with: Self-recorded by patient (classified by investigator criteria))											
1[1]	randomised trial	none	none	serious[2]	none[3]	none	41/54 (75.9%)	51/54 (94.4%)	RR 0.80 (0.68 to 0.95)	189 fewer per 1000 (from 47 fewer to 302 fewer)	LOW
Toxicity: At least one Class III adverse event (follow-up between instillations 1 and 9; assessed with: Self-recorded by patient (classified by investigator criteria))											
1[1]	randomised trial	none	none	serious[2]	none[3]	none	31/57 (54.4%)	44/58 (75.9%)	RR 0.72 (0.54 to 0.95)	212 fewer per 1000 (from 38 fewer to 349 fewer)	LOW
Health-related quality of life											
0	no evidence available										

[1] Colombel et al. (2006). BCG+ofloxacin versus BCG+placebo [2] Outcome of toxicity includes both local adverse events and systemic adverse events such as fever, myalgia, and fatigue, which limits the directness of this outcome to the review question [3] Small sample size and low number of events limits precision of outcome

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Table 69: GRADE evidence profile: The effectiveness of Isoniazid for the prevention of BCG-induced bladder toxicity in superficial bladder cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isoniazid	Control	Relative (95% CI)	Absolute	Quality
Bladder toxicity: Chemical cystitis (follow-up 12-18 months; assessed with: Patient report (Irritative bladder symptoms with negative urine culture))											
1[1]	randomised trial	none	none	none	serious[2]	none	113/256 (44.1%)	111/263 (42.2%)	RR 1.05 (0.86 to 1.27)	20 more per 1000 (from 59 fewer to 114 more)	MODERATE
Bladder toxicity: Frequency (follow-up 12-18 months; assessed with: Patient report)											
1[1]	randomised trial	none	none	none	serious[2]	none	144/256 (56.3%)	142/263 (54%)	RR 1.04 (0.89 to 1.22)	22 more per 1000 (from 59 fewer to 119 more)	MODERATE
Bladder toxicity: Macroscopic haematuria (follow-up 12-18 months; assessed with: Not specified)											
1[1]	randomised trial	none	none	none	serious[2]	none	78/256 (30.5%)	93/263 (35.4%)	RR 0.86 (0.67 to 1.1)	50 fewer per 1000 (from 117 fewer to 35 more)	MODERATE
Bladder toxicity (haematuria, dysuria, frequency) (follow-up 2 years; assessed with: Recorded by investigators)											
1[3]	randomised trial	none	none	none	serious[2]	none	28/80 (35%)	38/80 (47.5%)	RR 0.74 (0.51 to 1.07)	123 fewer per 1000 (from 233 fewer to 33 more)	MODERATE
Mild bladder toxicity (sub-group) (follow-up 2 years; assessed with: Recorded by investigators)											
1[3]	randomised trial	none	none	none	serious[4]	none	14/28 (50%)	5/38 (13.2%)	RR 3.80 (1.55 to 9.32)	368 more per 1000 (from 72 more to 1000 more)	MODERATE
Moderate bladder toxicity (sub-group) (follow-up 2 years; assessed with: Recorded by investigators)											
1[3]	randomised trial	none	none	none	serious[4]	none	7/28 (25%)	8/38 (21.1%)	RR 1.19 (0.49 to 2.89)	40 more per 1000 (from 107 fewer to 398 more)	MODERATE
Severe bladder toxicity (sub-group) (follow-up 2 years; assessed with: Recorded by investigators)											
1[3]	randomised trial	none	none	none	serious[4]	none	7/28 (25%)	25/38 (65.8%)	RR 0.38 (0.19 to 0.75)	408 fewer per 1000 (from 164 fewer to 533 fewer)	MODERATE
Health-related quality of life											
0	no evidence available										

[1] van der Meijden et al. (2001). BCG+isoniazid versus BCG alone [2] Wide confidence intervals and/or low number of events reduces the precision of this outcome; [3] Al Khalifa at al. (2000). BCG+isoniazid versus BCG+placebo [4] Low number of participants and events reduces the precision of this outcome

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Table 70: GRADE evidence profile: The effectiveness of Oxybutynin for the prevention of BCG-induced toxicity in superficial bladder cancer

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxybutynin	Placebo	Relative (95% CI)	Absolute	
Urinary symptoms											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	25	25	4	-	LOW
Systemic symptoms											
1[1]	randomised trials	serious[2]	none	none	serious[3]	none	25	25	5	-	LOW
Health-related quality of life											
0	No evidence available										

[1] Johnson et al. 2013 [2] Method of randomisation and allocation concealment not reported. [3] Small sample size (n=50). Number of events not reported. [4] Treatment group had greater increase in urinary frequency (p=0.004) and burning on urination compared to placebo (p=0.04). No significant differences in other urinary symptoms. [5] Treatment group reported increases in fever (p<0.0001), flu-like symptoms (p=0.0008), dry mouth (p=0.045) and constipation (p=0.001) compared to placebo.

Table 71: GRADE evidence profile: The effectiveness of reduced BCG dose for BCG-induced toxicity in superficial bladder cancer: 1/3 dose versus standard dose

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reduced dose BCG	Standard dose BCG	Relative (95% CI)	Absolute	
Bladder toxicity (assessed with: Local or systemic side-effects (1-yr treatment))											
1[1]	randomised trials	none	none	none	none	none	221/334 (66.2%)	228/329 (69.3%)	RR 0.95 (0.86 to 1.06)	35 fewer per 1000 (from 97 fewer to 42 more)	HIGH
Health-related quality of life											
0	No evidence available					none	-	-	-	-	

[1] Brausi et al. 2014

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Table 72: GRADE evidence profile: The effectiveness of formalin for the treatment of bladder haemorrhage secondary to radiation-induced cystitis

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Formalin	Control	Relative (95% CI)	Absolute	Quality
Bladder toxicity (follow-up 3-5 months; assessed with: Cessation of bleeding)											
2[1]	observational studies[2]	none	none	serious[3]	serious[4]	none	12/12 (100%)	-	-	-	VERY LOW
Health-related quality of life											
0	no evidence available					none	-	-	-	-	

[1] Likourinas et al. (1979); Kumar et al. (1975) [2] Case series [3] No information provided about cancer site, stage or grade in patients with radiation-induced bladder haemorrhage. Possibly non-bladder cancer patients. No details provided about radiation therapy received. [4] Small number of studies and participants limits the precision of this outcome

Table 73: GRADE evidence profile: The effectiveness of hyperbaric oxygen therapy (HBOT) for the treatment of radiation-induced hemorrhagic cystitis

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBOT	Control	Relative (95% CI)	Absolute	Quality
Bladder toxicity (follow-up 4 to 102 months; assessed with: resolution of haematuria)											
7[1]	observational studies[2]	none	serious[3]	serious[4]	none	none	94/153 (61.4%)	-	-	-	VERY LOW
Health-related quality of life											
0	no evidence available					none	-	-	-	-	

[1] Del Pizzo et al. (1998); Matthews et al. (1999); Corman et al. (2003); Parra et al. (2011); Weiss et al. (1994); Rijkmanset al. (1989); Lee et al. (1994) [2] Case series [3] Effectiveness ranged from 27% to 100% across studies [4] All studies included participants with prostate cancer and/or gynaecological cancers which limits the directness of the evidence to the population specified in the PICO

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Table 74: GRADE evidence profile: The effectiveness of sodium hyaluronate for the treatment of chemical-induced cystitis

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium hyaluronate**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Bladder capacity (millilitres) (follow-up 8 weeks; measured with: patient reported diary - mean of urinary volumes for at least 2 days; Better indicated by higher values)											
1[1]	observational studies[2]	none	none	serious[3]	none	none	54	-	Mean difference 226.1 (207.1 to 245)	-	VERY LOW
Pain (follow-up 8 weeks; measured with: Visual Analogue Scale (VAS); range of scores: 1-10; Better indicated by lower values)											
1[1]	observational studies[2]	none	none	serious[3]	none	none	54	-	Mean difference -7.7 (-8.12 to -7.31)	-	VERY LOW
Health-related quality of life											
0	no evidence available					-	-	-	-	-	

[1] Sommariva et al. (2010) [2] Case series [3] Out of 54 participants, 30 had received treatment with Mitomycin C and 24 had received intravesical BCG therapy, which limits the directness of the evidence to the population specified in the PICO

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Do not offer primary prophylaxis to prevent BCG-related bladder toxicity except as part of a clinical trial.** **Seek advice from a specialist urology multidisciplinary team if symptoms of bladder toxicity after BCG cannot be controlled with antispasmodics or non-opiate analgesia and other causes have been excluded by cystoscopy.** **Seek advice from a specialist urology multidisciplinary team if symptoms of bladder toxicity after radiotherapy cannot be controlled with antispasmodics or non-opiate analgesia and other causes have been excluded by cystoscopy.**
Relative value placed on the outcomes considered	Treatment-related toxicity and quality of life were both considered important outcomes despite the lack of evidence on quality of life. The GDG considered that quality of life would be improved by a reduction in bladder toxicity. Quality of life was not reported in the evidence.
Quality of the evidence	The quality of the evidence was assessed by GRADE as being of very low to high quality. Most of the publications were small case series studies, which are inadequate to assess this clinical scenario. The randomised trials that were identified were limited by a small sample size and low number of events. Many of the studies also included patients without a bladder cancer diagnosis which limits the relevance to the review question. The only outcome that was assessed as being of high quality reported no difference between reduced dose and normal dose BCG treatment. In the absence of high quality evidence about toxicity, the GDG were concerned about the detrimental effects of the interventions reported (e.g. ofloxacin and isoniazid) on the efficacy of BCG therapy. Due to this lack of evidence, the GDG based their recommendations on their clinical experience and consensus, and recommended that prophylaxis for BCG toxicity should not be offered outside of a clinical trial. The GDG agreed that there was insufficient evidence on which to base a recommendation about prophylaxis prior to radiotherapy. A recommendation for discussion with a specialist urology multidisciplinary team was made because the GDG could not make evidence-based recommendations for a specific treatment. There was no strong evidence to support a recommendation of prophylactic Ofloxacin or Isoniazid to prevent bladder toxicity, nor to reduce the dose or frequency of intravesical BCG. The GDG made a research recommendation because there is limited data that prophylactic treatment reduces BCG toxicity and there is also uncertainty about whether there could be a detrimental effect on the efficacy of the primary treatment (BCG therapy or radiotherapy).

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	The GDG felt it would be worth exploring this with further research but noted that future studies would need to have sufficient power in order to exclude non-inferiority. The GDG made both a research recommendation and the recommendation not to offer prophylactic treatment outside the context of a clinical trial. The GDG agreed that this recommendation was made to avoid the possibility that the primary treatment (BCG or radiotherapy) may be rendered less effective by prophylactic interventions.
Trade-off between clinical benefits and harms	The GDG considered that the potential benefits of their recommendations were avoiding unknown detrimental effects of prophylactic treatments and optimising management of patients in an evidence-poor area. The GDG considered that a potential clinical benefit from the recommendation is that the skills to treat patients with bladder toxicity will be centralised in specialised teams. The GDG considered that the lack of clear advice on what to do to prevent or treat radiation toxicity is a potential harm resulting from the recommendations. However, the GDG considered that it was best not to advise the use of unproven treatments that might worsen cancer outcomes.
Trade-off between net health benefits and resource use	There was no health economic evidence and an economic model was not developed for this topic. The GDG considered that less use of unproven preventative treatments would result in lower cost. The GDG considered that there would be an additional cost associated with seeking advice from specialist teams. However, earlier specialist team involvement may reduce extended local hospital stays, community care costs and the use of ineffective treatments.
Other considerations	Implementing the recommendations is unlikely to involve any equality issues. A potential change in clinical practice was identified by the GDG because the recommendations may result in increased involvement of specialist teams for uncommon but clinically difficult problems. The GDG also considered that the involvement of specialist teams may improve expertise within clinical practice.

Research recommendation	**Which interventions are effective in preventing or treating symptoms of bladder toxicity in people having BCG or radiation? A randomised trial should measure toxicity, quality of life, bladder cancer recurrence and progression.**
Why is this important	Radiotherapy and intravesical BCG can be effective in controlling or curing bladder cancer. Side effects, such as urinary frequency, urgency, bladder pain or bleeding can significantly worsen quality of life. The standard maintenance course of BCG is often not completed because of these side effects. The degree of the side effects following either treatment is occasionally so profound that cystectomy may be considered to alleviate them. There is no significant evidence that strategies commonly used to reduce side effects, such as reducing the dose, number of treatments, oral anticholinergics or prophylactic Ofloxacin, are effective.

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Research recommendation	Which interventions are effective in preventing or treating symptoms of bladder toxicity in people having BCG or radiation? A randomised trial should measure toxicity, quality of life, bladder cancer recurrence and progression.
	produce improved outcomes for toxicity and quality of life, without detriment to bladder cancer recurrence and progression

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

As discussed in section 4.1.2, non-muscle invasive bladder cancer can be divided into low, intermediate and high risk groups based on the risk of recurrence and progression.

Follow up of people with non-muscle invasive bladder cancer is done largely with periodic cystoscopy and the frequency of this is often adjusted according to the perceived degree of risk of the cancer. The scheduling of cystoscopy may be erratic due to lack of adherence to follow up protocols and waiting times. This adds extra stress to patients in addition to their anxiety about whether recurrence will be found.

Long term cystoscopic surveillance is expensive. The appropriate duration and frequency of cystoscopic follow up is unclear and in particular how it varies according to risk. Most follow up cystoscopies are likely to be done in people with low risk disease. Concern has been expressed whether current regimens are clinically and cost effective.

Urine cytology is also widely used in follow up of people with non-muscle invasive bladder cancer. Its sensitivity and specificity varies between risk groups but this is probably not taken into account in routine practice. In some hospitals urinary biomarkers are also used as well as or instead of urine cytology but this is not common practice.

Clinical question: What are the optimal follow-up protocols for low/intermediate risk and high-risk non-muscle invasive bladder cancer?

Clinical evidence (see also full evidence review)

The clinical evidence is summarised in tables 75 to 77.

Evidence statements

Moderate quality evidence from one randomised trial of 97 patients (Olsen & Genster, 1995) suggests uncertainty over whether cystoscopic follow-up frequency of three months is more or less effective than follow-up with a frequency of six months in terms of recurrence, progression or overall survival.

Low quality evidence from five observational studies of patients with low-grade superficial bladder cancer report recurrence rates over long-term follow-up. Two studies including 470 patients suggest that tumour detection at the first follow-up cystoscopy is associated with a greater risk of recurrence during subsequent follow-up compared to those who are tumour-free at the first cystoscopy (Holmang & Johansson 2002; Mariappan & Smith, 2005). All studies report a reduction in the risk of recurrence over time. Some studies suggest the risk of recurrences is greatly reduced after a tumour-free period of five years or more (Mariappan & Smith, 2005; Zieger *et al.*, 2000). In Mariappan & Smith (2005) only one (0.9%) patient had a first recurrence after being tumour-free for five years, whereas LeBlanc *et al.* (1999) reports recurrence rates of approximately 30% in patients after remaining tumour-free for two to ten years. Another study reports that of 20 primary Ta-T1 patients who were tumour-free for five years, seven (35%) had muscle-invasive disease (Thompson *et al.*, 1993).

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One retrospective observational study of 542 intermediate-high risk patients who had received BCG treatment reports that 338/542 (62%) patients were not tumour-free for five years or more. 22/204 (10.8%) patients had a recurrence after being tumour-free for five years or more (Holmang & Strock 2012). During the first five-years after BCG, 57 patients (10.5%) died from bladder cancer and between years six and 25, 32 patients (5.9%) died from bladder cancer.

Five observational studies report rates of upper urinary tract (UUT) recurrence ranging between 2.6% and 5.5%. Median times to UUT recurrence vary from 22 to 33 months in three studies (Miyake *et al.*, 2006; Canales *et al.*, 2006; Holmang *et al.*, 1998) and one study (Hession *et al.*, 1999) reports a mean time to recurrence of 78 months. In one study, two out of 18 UUT cancers were diagnosed by routine intravenous urography, and the other 18 presented with symptoms suggesting UUT recurrence before IVU (Miyake *et al.*, 2006). Holmang *et al.* (1998) reported that IVU performed 0 to ten months before the UUT cancer was diagnosed failed to raise suspicion of a tumour in eight out of 16 patients (including three patients with initial muscle-invasive bladder cancer).

Two studies provide low quality evidence of the accuracy of ultrasound compared with cystoscopy for the detection of recurrent tumours in patients with superficial bladder cancer. In one study, three tumours detected by cystoscopy were missed by ultrasound (Stamatiou *et al.*, 2011, and in the second study 15 patients with recurrence were not detected by ultrasound (Vallencien *et al.*, 1986).

Low quality evidence for health-related quality of life is provided by three studies (503 patients) which report that most patients experience minimal pain (Yossepowitch *et al.*, 2007) from undergoing cystoscopic follow-up, although the introduction of the cystoscope is rated as the most painful part of the procedure (van der Aa *et al.*, 2008). Waiting for test results is rated as the most distressing part of follow-up by urine testing (van der Aa *et al.*, 2008).

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Table 75: GRADE evidence profile: What are the optimal follow-up protocols for low/intermediate and high-risk non-muscle-invasive bladder cancer? Comparison: Frequent versus less frequent follow-up for TaG1-2 bladder cancer

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Frequent follow-up**	**Less frequent**	**Relative (95% CI)**	**Absolute**	**Quality**
Recurrence (follow-up 14.7 to 39.1 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	28/45 (62.2%)	26/52 (50%)	RR 1.24 (0.87 to 1.77)	120 more per 1000 (from 65 fewer to 385 more)	MODERATE
Progression (follow-up 14.7 to 39.1 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	3/45 (6.7%)	1/52 (1.9%)	RR 3.47 (0.37 to 32.17)	48 more per 1000 (from 12 fewer to 599 more)	MODERATE
Disease-specific mortality rate (follow-up 14.7 to 39.1 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	0/45 (0%)	0/52 (0%)	not pooled	not pooled	MODERATE
Overall mortality rate (follow-up 14.7 to 39.1 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	5/45 (11.1%)	2/52 (3.8%)	RR 2.89 (0.59 to 14.17)	73 more per 1000 (from 16 fewer to 507 more)	MODERATE
Treatment-related complications											
0	No evidence available										
Health-related quality of life											
0	No evidence available										
Patient experience/preference											
0	No evidence available										

[1] *Olsen & Genster 1995* [2] *Small number of events / confidence interval includes null value*

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Table 76: GRADE evidence profile: That are the optimal follow-up protocols for low/intermediate and high-risk non-muscle-invasive bladder cancer?

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Follow-up	Control	Relative (95% CI)	Absolute	Quality
Recurrence											
5[1]	observational studies	none	none	none	none	none	619/1125 (55%)	NA	-	-	LOW
Progression (assessed with: Progression in stage or grade)											
6[2]	observational studies	none	none	none	none	none	157/962 (16.3%)	NA	-	-	LOW
Recurrence (Upper Urinary Tract)											
5[3]	observational studies	none	none	none	none	none	102/2360 (4.3%)	NA	-	-	LOW
Overall mortality rate (Intermediate/high risk NMIBC) (follow-up 5 to 25 years)											
1[4]	observational studies	none	none	none	none	none	335/542 (61.8%)	NA	-	-	LOW
Disease-specific mortality (Ta NMIBC) (follow-up mean 84 months)											
1[5]	observational studies	none	none	none	none	none	23/217 (10.6%)	NA	-	-	LOW
Disease-specific mortality (Intermediate/high risk NMIBC) (follow-up 5 to 25 years)											
1[4]	observational studies	none	none	none	none	none	89/542 (16.4%)	NA	-	-	LOW
Treatment-related complications											
0	No evidence available										
Health-related quality of life											
0	No evidence available										
Patient experience/preference											
3[6]	observational studies	none	none	none	none	none	503	-	See Table 66		LOW

[1] Mariappan & Smith 2005; LeBlanc et al. 1999; Zieger et al. 2000; Oge et al. 2000; Holmang & Strock 2012 [2] Mariappan & Smith 2005; LeBlanc et al. 1999; Zieger et al. 2000; Oge et al. 2000; Thompson et al. 1993; Holmang et al. 2012 [3] Miyake et al. 2006; Holmang et al. 1998; Hession et al. 1999; Canales et al. 2006; Sternberg et al. 2013 [4] Holmang & Strock 2012 [5] Zieger et al. 2000 [6] Yossepowitch et al. 2007; Van der Aa et al. 2008; Vriesema et al. 2000

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Table 77: Patient experience and preference for follow-up of NMIBC

Study	Patients	Results
Yossepowitch et al. 2007	200 NMIBC undergoing flexi cystoscopy follow-up	Pain: 74% reported minimal or no pain. Higher pain ratings from those undergoing fulguration compared to those undergoing cystoscopy alone.
Van der Aa et al. 2008	201 NMIBC undergoing 3-monthly flexible cystoscopy and urinal microsatellite analysis	Discomfort: introduction of the cystoscope was most uncomfortable and painful part of cystoscopy and awaiting the result was the most distressing time of urine test.
Vriesema et al. 2000	102 NMIBC undergoing flexi cystoscopy follow-up	Bothersome: Not bothersome 29/85 (34%); somewhat bothersome 45/85 (53%); very bothersome 11/85 (13%). No differences in ratings by age or gender.

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Cost-effectiveness evidence (see also Appendix B)

Background

There is general agreement that patients with non-muscle invasive bladder cancer (NMIBC) require regular cystoscopic surveillance of their bladder to check for recurrence. However, there is no agreement upon the optimal frequency and length of cystoscopic follow-up and, as such, there is significant variation in clinical practice.

Tailoring follow-up strategies based on risk could allow for follow-up to be safely reduced in the lower risk groups whilst ensuring that the higher risk patients are still monitored closely. In addition, the use of alternative tests to cystoscopy, such as urinary biomarkers and cytology, could have a useful role in reducing the burden of cystocopies. However, the effectiveness and cost-effectiveness of such approaches has never been reliably demonstrated.

Aims

To estimate the cost-effectiveness of reduced follow-up and/or follow-up using newer tests and techniques in comparison to the test and protocols used in current practice in NMIBC patients.

Existing Economic Evidence

A systematic literature review did not identify any cost-utility analyses that sufficiently addressed the current decision problem. However, three papers were identified that utilised modelling techniques to compare follow-up strategies; De Bekker Grob et al. 2009, Van Kessel et al. 2013 and Zhang et al. 2013.

De Bekker Grob et al. 2009 constructed a semi-Markov model to investigate two strategies; a conventional strategy consisting of cystoscopy every 3 months and a test arm consisting of microsatellite analysis of voided urine samples every 3 months with a control cystoscopy at 3, 12 and 24 months. The authors found that the probability of being without recurrence after 2 years was similar in the two groups but the total costs were higher in the test arm. Further analysis suggested that the test arm would be as effective and cost the same as the conventional arm if the sensitivity increased to ≥61%, the specificity was set to 73% and the costs were decreased from €158 to <€70. The authors concluded that cystoscopy could be partly replaced if the microsatellite analysis urine test had a higher sensitivity and its costs were reduced.

A similar analysis was conducted by Van Kessel et al. 2013, in which three surveillance strategies were compared using a Markov model; standard surveillance defined as cystoscopy every three months, minimal surveillance defined as cystoscopy at 3, 12 and 24 months and modified surveillance consisting of FGFR3 mutation analysis of voided urine samples every 3 months and cystoscopy at 3, 12 and 24 months. The authors found that the probability of no recurrence after two years of surveillance was higher for the modified surveillance than the standard or minimal surveillance arms. The total cost of surveillance was found to be lower for minimal and modified surveillance than for standard surveillance. The authors concluded that surveillance in which cystoscopy is partly replaced by FGFR3 mutation analysis of urine seems a safe, effective and cost-effective surveillance strategy.

The analysis conducted by Zhang et al. 2013 compared surveillance strategies for low risk NMIBC patients. The study was not a cost-effectiveness analysis and indeed did not even consider costs but it did estimate QALYs for each strategy. The authors developed a Markov model to compare surveillance strategies recommended in international guidelines and additional proposed strategies. The authors found that age and co-morbidities significantly affect the optimal surveillance strategy. The results suggested that younger patients should

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be screened more intensively than older patients and patients with co-morbidities should be screened less intensively.

De Novo Economic Model

Since the current economic literature didn't adequately address the decision problem[d], a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel.

Patients were assumed to enter the model in a 'disease free' state following an initial transurethral resection of the bladder tumour (TURBT). At each 3-monthly model cycle the patient may experience a bladder cancer recurrence. If the recurrence is detected, the patient will undergo a further TURBT (or fulguration of the tumour) and return to a disease free state. However, if the recurrence is not detected, then the patient will be at risk of progression and will have to undergo further treatment once this progression is eventually detected (cystectomy and possibly neo-adjuvant chemotherapy). The patient may also die from bladder cancer related mortality after experiencing progression and may die from other cause mortality from any health state.

Estimated total costs and quality adjusted life years (QALYs) were collected over the modelled 10 year time horizon for each follow-up strategy. Future costs and benefits were discounted at a rate of 3.5% per year as recommended by NICE.

The risk of recurrence and progression in patients with NMIBC was estimated using risk equations based on an analysis of 2,596 patients from seven EORTC[e] trials (Sylvester et al. 2006). Patients are 'scored' based on a number of risk factors, such as number of tumours, tumour size, prior recurrence rate, T category, presence of CIS and grade. An individual's one year and five year risks of recurrence and progression can then be estimated based upon these scores.

For the purposes of the economic model, it was necessary to convert these five year and one year risks into 3-monthly risks. The higher risk of recurrence and progression in the first year was captured by calculating separate 3 monthly risks for the first year and subsequent years (based on the one year risk and five year EORTC risks). Furthermore, since the EORTC risk equations consider recurrence and progression independently, it was necessary to link the progression rates to the recurrence rate i.e. estimate the probability of progression given recurrence in each of the risk groups.

Table 78 shows the three monthly risks of recurrence, progression and progression given recurrence applied for each of the risk groups in the base case analysis.

Table 78: Three monthly recurrence and progression risk applied in the model

Outcome	3 monthly rates		
	Recurrence	Progression given recurrence	Progression
First year			
Low risk	3.98%	1.26%	0.05%
Intermediate risk	6.63%	3.78%	0.25%
High risk – Lower	11.26%	11.31%	1.27%
High risk – Upper	20.97%	21.70%	4.55%
Subsequent years			
Low risk	1.84%*	2.18%*	0.04%*
Intermediate risk	3.03%	10.18%	0.31%

[d] It should be noted that, while none of the above studies met the requirements for inclusion in the systematic review, they were nonetheless informative in helping to develop our own de novo economic model.
[e] European Organisation for Research and Treatment of Cancer

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Outcome	3 monthly rates		
High risk – lower	4.72%	19.64%	0.93%
High risk – upper	7.29%	40.39%	2.94%

**In low risk patients, rates of recurrence and progression in years 6-10 are assumed to be zero*

As the modelled time horizon of 10 years exceeds the predicted risk estimates from the EORTC trials (5 years), it was also necessary to make some assumptions about the risk profile of patients in years 5-10. In the base case, it was assumed that the subsequent year rate (i.e. years 2-5) would be maintained in years 6-10 except in the case of low-risk patients in whom it was assumed that risk would be zero after 5 years (reflecting clinical practice of discharging low-risk patients from follow-up after 5 years).

Bladder cancer related mortality rates were estimated using data from a systematic review by Van den Bosch et al. 2011. Using the data in the study, separate three mortality rates were estimated for patients that progressed to muscle invasive disease and those that remained non-muscle invasive following a cystectomy (3.6% and 0.5%, respectively). The lower rate in NMIBC patients reflects an assumption that patients would have to first progress to MIBC before dying of bladder cancer.

Death from other causes was captured using 2009-2011 life tables for England and Wales from the Office of National Statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender with the model assuming that 50% of patients were female and that the average age was 60 years old. These annual probabilities were converted to three-monthly probabilities for use in the model.

Follow-up strategies

The variations in the frequency of follow-up that were considered in the model are summarised in table 79.

Table 79: Follow up strategies

Risk group	Follow-up strategy		
	Current practice	Slightly reduced frequency	Reduced frequency
Low risk	Cystoscopy at 3 months, 1 year and annually thereafter	Cystoscopy at 3 months and annually thereafter	Cystoscopy at 3 months, 1 year and then discharge
Intermediate risk	Cystoscopy every 3 months for 2 years, then every 6 months for 2 years and annually thereafter	Cystoscopy every 3 months for 1 year, then 6 monthly for 2 years and annually thereafter	Escalating intervals up to 1 year, with cystoscopy at 3 months, 9 months, 18 months, 30 months and annually thereafter.
High risk	Cystoscopy every 3 months for 2 years, then every 6 months for 2 years and annually thereafter	Cystoscopy every 3 months for 2 years and annually thereafter	Cystoscopy every 3 months for 1 year, then 6 monthly for 1 year and annually thereafter

In addition to these variations, the use of a urinary biomarker (FISH) or cytology as a safety net to detect recurrences at the time points that would normally be checked under current practice was also considered. The diagnostic accuracy of these tests as well as cystoscopy were estimated using data from the systematic review of the clinical evidence conducted for this guideline, with most data being sourced from a systematic review by Mowatt et al. 2010.

Costs and utilities

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective

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of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. GP visit). Where possible, all costs were estimated in 2012-13 prices.

The majority of costs were sourced from NHS reference costs 2012/13 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dosages from the British National Formulary (BNF) and unit cost information from the electronic market information tool (eMit). Where unit costs for drugs were not available from eMit, prices from the BNF were used. Resource use and cost information were obtained from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs were estimated by combining the life year estimates with utility values (or QOL weights) associated with being in a particular health state. These utility values were identified through a search of the available literature.

Base Case Results

The base case results of the analysis for are presented in table 80 for patients in each risk category. The results are shown in the 'dominance rank' format as it allows for the best overall strategy to be evaluated.

Table 80: Base case cost-effectiveness result using dominance rank

Follow-up strategy	Cost		QALYs		Cost per QALY
	Total	Incremental	Total	Incremental	
Low risk					
Reduced frequency	**£4,805**	**-**	**6.26**	**-**	**-**
Cytology w/ reduced frequency	£7,206	£2,401	6.29	0.0307	£78,310
FISH w/ reduced frequency	£8,024	£3,219	6.29	0.0383	£83,9990
Slightly reduced frequency	£8,675	£3,869	6.29	0.0371	£104,392
Current practice	£8,845	£4,040	6.29	0.0381	£106,019
Intermediate risk					
Reduced frequency	**£17,037**	**-**	**6.15**	**-**	**-**
Cytology w/ reduced frequency	£18,998	£1,961	6.19	0.0420	£46,660
Slightly reduced frequency	£19,970	£2,933	6.18	0.0320	£91,762
FISH w/ reduced frequency	£20,531	£3,494	6.21	0.0560	£85,511
Cytology w/ slightly reduced frequency	£20,539	£3,502	6.19	0.0409	£62,574
FISH w/ slightly reduced frequency	£21,000	£3,962	6.20	0.0456	£86,845
Current practice	£21,988	£4,950	6.20	0.0454	£108,925
High risk					
Reduced frequency	£26,637	-	5.40	-	-
Cytology w/ reduced frequency	£26,903	£266	5.48	0.0720	£3,698
FISH w/ reduced frequency	**£27,112**	**£209**	**5.52**	**0.0409**	**£5,095**
Slightly reduced frequency	£27,227	£115	5.47	-0.0487	Dominated
Cytology w/ slightly reduced frequency	£27,362	£250	5.50	-0.0184	Dominated
FISH w/ slightly reduced frequency	£27,459	£347	5.52	-0.0009	Dominated
Current practice	£27,674	£563	5.52	-0.0016	Dominated

It can be seen that the optimal strategy in low and intermediate risk patients is the reduced frequency strategy. This strategy is the least effective of all the strategies but the difference is marginal and because it is substantially cheaper than the other strategies it was found to be cost-effective overall.

In the case of high risk patients, it can be seen that the reduced frequency strategy is again the cheapest strategy but it is no longer the preferred strategy in cost-effectiveness terms.

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Strategies of reduced frequency with a safety net using FISH or cytology were found to be more cost-effective than this strategy with the reduced frequency follow-up strategy with FISH found to be the most cost-effective (more cost-effective than cytology because of the superior sensitivity of FISH in the base case).

Sensitivity analysis

A series of one-way sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result.

The analyses showed that, in low and intermediate risk patients, reduced frequency follow-up was the most cost-effective strategy in all modelled scenarios. In the case of high risk patients, the optimal strategy remains the same as in the base case (i.e. reduced frequency with FISH) in the vast majority of the analyses. However, there are two exceptions where the reduced frequency follow-up becomes the most cost-effective strategy; one where the modelled time horizon is reduced to five years and another where the bladder cancer specific mortality rates are equivalent for NMIBC and MIBC patients.

The GDG were also interested in an analysis where only variations in follow-up frequency were considered (i.e. variations in diagnostic tests were excluded from the analysis). As in the full analysis, it was found that the optimal strategy in low and intermediate risk patients was the reduced frequency strategy. However, in the case of high risk patients, the cystoscopy frequency used in current practice was found to be the most cost-effective strategy with a cost per QALY of £9,487 in comparison to the next based strategy (Slightly reduced follow-up).

A probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case were replaced with values drawn from distributions around the mean values. It was found that, at a threshold of £20,000 per QALY, the reduced frequency follow-up strategy had a 98% and 91% probability of being cost-effective in the low and intermediate risk group, respectively. In high risk patients it was found that, at a threshold of £20,000 per QALY, the reduced follow-up strategy in combination with FISH had a 79% probability of being cost-effective.

Conclusion

The results of the analysis suggest that reducing the frequency of cystoscopic follow-up in low and intermediate risk patients is cost-effective. Furthermore, the results show that the addition of cytology or FISH as a safety net was not cost-effective in these risk groups. In high risk patients, the results of the analysis suggest that reducing cystoscopic follow-up alone is not cost-effective in comparison to current practice. However, the addition of cytology or FISH as a safety net was found to be cost-effective with a reduced frequency follow-up strategy with FISH found to be the most cost-effective strategy.

However, there are concerns about the lack of comparative data that investigates variations in follow-up and further research is required to fully assess the safety, effectiveness and cost-effectiveness of the proposed follow-up strategies.

Recommendations	**Offer people with low-risk non-muscle-invasive bladder cancer cystoscopic follow-up 3 months and 12 months after diagnosis.** **Discharge to primary care people who have had low-risk non-muscle-invasive bladder cancer and who have no recurrence of the bladder cancer within 12 months.**

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	Do not offer routine urinary cytology or prolonged cystoscopic follow-up after 12 months for people with low-risk non-muscle-invasive bladder cancer. **Offer people with intermediate-risk non-muscle-invasive bladder cancer cystoscopic follow-up at 3, 9 and 18 months, and once a year thereafter.** **Consider discharging people who have had intermediate-risk non-muscle-invasive bladder cancer to primary care after 5 years of disease-free follow-up.** **Offer people with high-risk non-muscle-invasive bladder cancer cystoscopic follow up:** • **every 3 months for the first 2 years then** • **every 6 months for the next 2 years then** • **once a year thereafter.** **Refer people urgently to urological services if they have haematuria or other urinary symptoms and a history of non-muscle-invasive bladder cancer.**
Relative value placed on the outcomes considered	The GDG considered the following outcomes to be important: Progression is associated with morbidity, mortality and cost and is readily captured; Disease specific survival and overall survival are important outcomes because it is important not to have avoidable death; Quality of life is important because it captures the patient experience of both the intervention and the disease. Patient preference, treatment-related complications, and health-related quality of life were specified as outcomes in the PICO but were not reported in the evidence. No further outcomes were used to make recommendations.
Quality of the evidence	The evidence was assessed as being of low to moderate quality using GRADE The evidence was limited by a general lack of high quality evidence. Many of the included studies were old studies and had small sample sizes, low number of events and different patient populations. The GDG considered that there was insufficient evidence to be able to support recommendations for radical changes to follow-up for patients with high-risk bladder cancer. For low and intermediate risk groups, the clinical experience of the group and the limited evidence available were felt to be sufficient to make recommendations for a change in practice. A research recommendation was made although there was a suggestion in the cost-effectiveness model that changes in follow-up in patients with high-risk disease could be safe and cost-effective. However, as there was no robust evidence in clinical practice the GDG did not feel that it could be introduced as a new standard of care and so felt that a research recommendation was appropriate. The recommendation in patients with high-risk disease results from the group's consensus estimation of conservative current practice supported by the economic model. The research recommendation sought to assess new models of follow-up.
Trade-off between	The potential benefits of the recommendation for patients with low risk

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clinical benefits and harms	disease result from the reduced burden of cystoscopic follow-up. The GDG balanced this against the potential for harm resulting from a possible small increase in the late detection of disease recurrence and that patients may experience anxiety after discharge from follow-up. The GDG considered that reducing the burden of follow-up strongly outweighs the possible increase in late detection of recurrence. For patients with intermediate and high-risk disease, benefits may result from the wider implementation of standard practice (reduction in variation in practice), more effective identification of progression, and decreased patient anxiety from more frequent follow-up. The GDG balanced this against the possible increase in morbidity associated with cystoscopies and an increase in patient anxiety from an increased number of cystoscopies. The GDG prioritised reduction in variation in practice. The GDG also considered that minimising progression is a priority in these groups due to the adverse impact of progressive disease on patient health.
Trade-off between net health benefits and resource use	A health economic model was developed for this topic. The results of the economic analysis showed that the optimal follow-up strategy varied in each risk group: Low and intermediate risk Reduced frequency follow-up was shown to be the most cost-effective strategy in low and intermediate risk patients. It was less effective in QALY terms than the other strategies but substantially cheaper and so overall the strategy was found to be cost-effective (i.e. all other strategies have ICER > £20,000 per QALY in comparison to reduced frequency follow-up). High risk FISH with reduced frequency follow-up was shown to be the most cost-effective strategy in high risk patients. It was found to be one of the cheapest strategies and the most effective in QALY terms. In the dominance rank, it was shown to have an ICER of £5,095 per QALY in comparison to the next best strategy (cytology with reduced frequency). Owing to practical issues regarding the regular use of urinary biomarkers and cytology, the GDG were also interested in a sensitivity analysis where FISH and cytology were excluded (i.e. variations in frequency only). The results showed the current practice schedule to be the most cost-effective. It was found to be more expensive than reduced frequency schedules but was cost-effective with an ICER < £20,000 per QALY. The results of the economic model enabled the GDG to reduce the frequency and duration of cystoscopy in low and intermediate risk and informed the research recommendation in high risk patients. Overall, the GDG anticipated that the recommendations could have the following impact on costs: Low and intermediate risk Potential for increased costs associated with treating otherwise avoidable disease.

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	Also, likely to be increased costs associated with follow-up by GPs. There will be substantial savings from reduced cystoscopic follow-up in low and intermediate risk patients High risk Potential for higher costs in some instances as the 'current practice' schedule may be more intensive than that used by some centres. The earlier detection of bladder cancer may lead to potential for savings through reduced treatment of advanced bladder cancer. Further savings could be made by substituting urinary tests for cystoscopy.
Other considerations	No equalities issues were identified. The GDG considered the potential change in practice resulting from these recommendations includes a substantial reduction in cystoscopic follow-up in low risk disease, an increased role in follow-up for GPs, and some reduction in cystoscopic follow-up for patients with intermediate risk disease. The GDG considered it difficult to assess the extent to change in practice required to implement the recommendation for patients with high-risk disease because of uncertainty over current practice. However, implementing the recommendations will require a risk assessment, which will be a change compared to current practice. The GDG were uncertain about what follow-up regimens are currently in place across the NHS. Strategies involving FISH were attractive in cost-effectiveness terms but there was uncertainty about their effectiveness as a substitute for cystoscopy and there was a concern about a lack of availability of the test within the NHS. After much debate, the GDG decided it was best to consider using urinary tests in a research setting rather than recommend immediate implementation. The GDG discussed how these recommendations could be audited and monitored, particularly in low risk patients.

Research recommendation	**In people with high-risk non-muscle-invasive bladder cancer, are these follow-up regimens equally effective in terms of identification of progression, cost effectiveness and health-related quality of life?** • **Cystoscopic follow-up at 3, 6, 12, 18, 24, 36 and 48 months, and then annually, interspersed with non-invasive urinary tests.** • **Cystoscopic follow-up at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42 and 48 months and then annually thereafter.**
Why is this important	Cystoscopy is currently the standard of care for follow-up of people with high-risk non-muscle-invasive bladder cancer. Regular cystoscopy may be associated with anxiety, procedural discomfort to the person and significant costs to the NHS. Urine tests based on a variety of technologies (including cytology,

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	fluorescence in-situ hybridization [FISH] and proteomic platforms) can detect high-grade recurrence, raising the possibility that 1 or more of these tests could be used to reduce the frequency of cystoscopy. This could improve acceptability to patients and reduce costs to the NHS without increasing the risk of disease progression. There is a lack of evidence on the optimal frequency of follow-up and whether the frequency of cystoscopy follow-up can safely be reduced by substitution of urinary tests.

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5 Managing muscle-invasive bladder cancer

About a quarter of all people with bladder cancer have cancer in the muscle wall of the bladder (muscle invasive bladder cancer, or MIBC). This has a high risk of spread and presents an immediate threat to life. In about 20 to 25 out of 100 people with MIBC who have had surgery to remove the bladder (radical cystectomy), microscopic spread to the lymph nodes is found. This is therefore likely to be the case in people with MIBC who have radical radiotherapy. Spread to the lymph nodes usually reduces the chance of cure considerably. Treatment options for people with MIBC are therefore directed at both the cancer in the bladder and at possible unsuspected spread to lymph nodes. The options considered are chemotherapy, radical cystectomy and radical radiotherapy. There is uncertainty over the relative effectiveness and indications for each of these treatments which contributes to considerable variation in UK practice.

5.1 The role of chemotherapy in treatment of organ confined muscle-invasive bladder cancer

If the bladder cancer has invaded the muscle of the bladder wall, then there is a very high risk that the patient will die of bladder cancer unless radical treatment with either radical cystectomy or radical radiotherapy is done. Although radical cystectomy or radical radiotherapy offers the best chance of cure, unfortunately up to half of these people still go on to die of bladder cancer. This is usually due to the cancer returning in the region of the bladder, existing unsuspected spread to lymph nodes or, more typically, recurrence in other parts of the body such as the lymph nodes, lungs, liver or bones. For many cancers this risk of relapse can be reduced or delayed by giving chemotherapy before and/or after surgery or radical radiotherapy. However, these treatments are associated with significant side effects. These side effects may be more problematic in people with other illnesses or people who are generally less fit.

5.1.1 Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is given before surgery or radical radiotherapy. It is believed that neoadjuvant chemotherapy may act by eradicating unrecognised micro-metastatic disease. There are two commonly used regimens but there is uncertainty over which is the most clinically effective. There is no consensus on which patients would benefit most from neoadjuvant chemotherapy.

Clinical question: Which patients with bladder cancer should be offered neoadjuvant chemotherapy?

Clinical evidence (see also full evidence review)

Evidence is summarised in table 81.

Evidence statements

One systematic review and meta-analysis of individual patient data (3,005 patients from 11 randomised trials) was identified (Advanced Bladder Cancer Meta-Analysis Collaboration (ABC), 2004). No other randomised trials were identified. High quality evidence about overall survival came from 10 trials with a total of 2,809 patients. There was no clear evidence of statistical heterogeneity (p=0.47) or inconsistency between trials (I^2=0%). All trials were reported to have adequate allocation concealment at randomisation. The pooled hazard ratio (HR) of 0.89 (95% CI 0.81 to 0.98) for these trials represents an 11% relative reduction in the risk of death associated with neoadjuvant chemotherapy. This is equivalent to an

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absolute improvement of 4% at five years (95% CI 0% to 7%), increasing overall survival from 45% to 49%.

When trials were grouped by chemotherapy type there was uncertainty about the effect of single-agent cisplatin on overall survival, as the 95% confidence interval of the effect estimate included the null value (HR 1.15, 95% CI 0.90 to 1.47). The pooled HR for trials using combination chemotherapy was 0.86 (95% CI 0.77 to 0.95), equivalent to a 14% relative reduction in the risk of death with neoadjuvant chemotherapy; an absolute benefit of 5% at five years (95% CI 2% to 9%), improving survival from 45% to 50%.

The trials of combination chemotherapy were grouped by planned local treatment: cystectomy alone, radical radiotherapy alone, or combined radiotherapy and cystectomy. There was no evidence of a difference in the effect of chemotherapy in the three local treatment groups (interaction p=0.656).

10 trials including 2,486 patients and 1,847 events (1,606 (87%) recurrences and 241 (13%) deaths) provided high quality evidence on disease-free survival, with a HR of 0.81 (95% CI 0.74 to 0.89) in favour of neoadjuvant chemotherapy. When grouped by chemotherapy type, moderate quality evidence from two trials showed no statistically significant effect of single-agent cisplatin on disease-free survival, as the 95% confidence intervals of the effect estimate included the null value (HR 1.14, 95% CI 0.83 to 1.55). The pooled HR for trials using combination chemotherapy was 0.78 (95% CI 0.71 to 0.86), equivalent to a 22% relative reduction in the risk of locoregional recurrence, metastases or death with neoadjuvant chemotherapy; an absolute disease-free survival benefit of 9% at five years (95% CI 5% to 12%).

For metastases-free survival, data from seven trials including 2,180 patients and 1,345 events were available. The numbers of events in each group were not provided in the systematic review. The pooled results for metastases-free survival shows a similar pattern to survival, both in terms of chemotherapy type and local treatment, with a significant benefit of platinum-based combination chemotherapy (HR 0.82, 95% CI 0.73 to 0.92); an absolute metastases-free survival benefit of 7% (95% CI 3% to 11%).

The systematic review states that there was insufficient data to formally investigate toxicity or health-related quality of life in these trials. However, where it was reported in the publications, the most common chemotherapy-related toxicities included nausea and vomiting, haematological toxicities, and impaired renal function.

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Table 81: GRADE evidence profile: Which patients with bladder cancer should be offered neoadjuvant chemotherapy?

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant CT + local treatment	local treatment only	Relative (95% CI)	Absolute	Quality
Overall survival											
10[1]	randomised trials	none	none	none	none	none	822/1406 (58.5%)	881/1420 (62%)	HR 0.89 (0.81 to 0.98)	4% (95% CI 0% to 7%) improvement of 5 yr survival from 45% to 49%	HIGH
Overall survival by chemotherapy type - Single agent platinum											
3[1]	randomised trials	none	none	none	serious[2]	none	136/186 (73.1%)	137/207 (66.2%)	HR 1.15 (0.9 to 1.47)	5% (95% CI -14% to 4%) reduction of 5 yr survival	MODERATE
Overall survival by chemotherapy type - Platinum-based combination											
7[1]	randomised trials	none	none	none	None	none	686/1220 (56.2%)	744/1213 (61.3%)	HR 0.86 (0.77 to 0.95)	5% (95% CI 2% to 9%) improvement of 5 yr survival from 45% to 50%	HIGH
Overall survival by treatment type											
7[1]	randomised trials	none	none	none	None	none	683/1214 (56.3%)	739/1207 (61.2%)	HR 0.86 (0.77 to 0.95)	-	HIGH
Overall survival by treatment type – Cystectomy											
6[1]	randomised trials	none	none	none	None	none	413/762 (54.2%)	444/746 (59.5%)	HR 0.86 (0.75 to 0.98)	-	HIGH
Overall survival by treatment type – Radiotherapy											
2[1]	randomised trials	none	none	none	serious[2]	none	184/263 (70%)	189/263 (71.9%)	HR 0.91 (0.74 to 1.11)	-	MODERATE
Overall survival by treatment type - Radiotherapy + cystectomy											
2[1]	randomised trials	none	none	none	serious[2]	none	86/189 (45.5%)	106/198 (53.5%)	HR 0.77 (0.58 to 1.02)	-	MODERATE
Disease-free survival											
10[1]	randomised trials	none	none	none	None	none	875/1419 (61.7%)	972/1427 (68.1%)	HR 0.81 (0.74 to 0.89)	8% improvement (95% CI 4% to 11%)	HIGH
Disease-free survival by chemotherapy type - Single agent cisplatin											
2[1]	randomised trials	none	none	none	serious[2]	none	81/103 (78.6%)	85/114 (74.6%)	HR 1.14 (0.83 to	5% reduction (95% CI -16% to 7%)	MODERATE

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Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant CT + local treatment	local treatment only	Relative (95% CI)	Absolute	Quality
									1.55)		
Disease-free survival by chemotherapy type - Platinum-based combination											
8[1]	randomised trials	none	none	none	None	none	794/1316 (60.3%)	887/1313 (67.6%)	HR 0.78 (0.71 to 0.86)	9% improvement of 5 yr survival (95% CI 5% to 12%)	HIGH
Disease-free survival by treatment type – Cystectomy											
Not reporter	randomised trials	none	none	none	None	none	Not reported	Not reported	HR 0.75 (0.66 to 0.84)	-	HIGH
Disease-free survival by treatment type – Radiotherapy											
Not reporter	randomised trials	none	none	none	serious[2]	none	Not reported	Not reported	HR 0.92 (0.76 to 1.11)	-	MODERATE
Disease-free survival by treatment type - Radiotherapy + cystectomy											
Not reporter	randomised trials	none	none	none	None	none	Not reported	Not reported	HR 0.71 (0.54 to 0.94)	-	HIGH
Metastases-free survival											
7[1]	randomised trials	none	none	none	None	none	Not reported	Not reported	HR 0.86 (0.77 to 0.95)	5% improvement (95% CI 2% to 9%)	HIGH
Metastases-free survival by chemotherapy type - Single agent platinum											
Not reported[1]	randomised trials	none	none	none	serious[2]	none	Not reported	Not reported	HR 1.21 (0.88 to 1.67)	7% reduction (95% CI -18% to 5%)	MODERATE
Metastases-free survival by chemotherapy type - Platinum based combination											
Not reported[1]	randomised trials	none	none	none	serious[3]	none	Not reported	Not reported	HR 0.82 (0.73 to 0.92)	7% improvement (95% CI 3% to 11%)	MODERATE
Metastases-free survival by treatment type – Cystectomy											
Not reported[1]	randomised trials	none	none	none	serious[3]	none	Not reported	Not reported	HR 0.82 (0.70 to 0.96)	-	MODERATE
Metastases-free survival by treatment type – Radiotherapy											
Not reported[1]	randomised trials	none	none	none	serious[2]	none	Not reported	Not reported	HR 0.87 (0.71 to 1.06)	-	MODERATE
Metastases-free survival by treatment type - Radiotherapy + cystectomy											
Not	randomised	none	none	none	serious[3]	none	Not reported	Not	HR 0.73	-	MODERATE

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Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Neoadjuvant CT + local treatment**	**local treatment only**	**Relative (95% CI)**	**Absolute**	
reported[1]	trials							reported	(0.56 to 0.97)		
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Health related quality of life											
0	No evidence available										

[1] From Advanced Bladder Cancer Meta-Analysis Collaboration (ABC) systematic review (2004) [2] Wide confidence interval (including null value) and/or low number of events limits the precision of this outcome [3] Number of studies, events and participants not reported

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer neoadjuvant chemotherapy using a cisplatin combination regimen before radical cystectomy or radical radiotherapy to people with newly diagnosed muscle-invasive urothelial bladder cancer for whom cisplatin-based chemotherapy is suitable. Ensure that they have an opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer.**
Relative value placed on the outcomes considered	All outcomes from the PICO were considered important by the GDG. Overall survival and disease-free survival are the most reliable and important indicators of clinical benefit. Quality of life is important for the patient. Quality of life and treatment-related mortality were specified as outcomes in the PICO but were not reported in the evidence. No additional outcomes were used by the GDG to make recommendations.
Quality of the evidence	The quality of the evidence was moderate to high as assessed with GRADE. The evidence was limited by the outdated regimens that were used in the trials and there have since been improvements in radical therapy. The GDG considered that modern regimens are at least as effective as those in the trials. The benefits reported in the evidence should be seen as the minimum gain that modern day patients should expect. As the effects of neoadjuvant chemotherapy are on distant disease control it is unlikely that improvements in radical treatment would impact on this effect. A research recommendation was made because current subgroup definitions do not predict clinical benefits. The evidence presented suggests that the patient group as a whole benefits from neoadjuvant chemotherapy but the GDG recognised that it is likely that not all patients benefit equally. For instance, some data suggests that patients who attain a complete response to chemotherapy are most likely to have a survival benefit and non responders are unlikely to benefit. If the subgroups that did not benefit could be identified between treatment, intensive treatment with significant side effects could be avoided and definitive local treatment be administered immediately. Research to better target treatment could therefore improve treatment delivery and the patient experience.
Trade-off between clinical benefits and harms	The GDG weighed up the clinical benefits of improved clinical outcomes in patients with MIBC who are suitable for cisplatin-based chemotherapy against the harm of the toxicity of additional chemotherapy and prioritised the survival benefit. The GDG considered that increased survival outweighs short-term toxicity.

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Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG considered the potential costs of the recommendation arise from the chemotherapy delivery and management of toxicity. The potential savings include cessation of best supportive care. Neoadjuvant chemotherapy will improve survival and is therefore likely to be cost-effective. The GDG considered that the QALY gain is likely to be sufficient to make the recommendation cost-effective
Other considerations	The GDG considered that there are no equalities issues as the recommendations would still consider those with hearing impairments for neoadjuvant chemotherapy. The GDG was unsure of the extent of change in practice required to implement the recommendation. Specialist and patient choice were considered in the recommendation. The GDG considered a 'do not use' recommendation regarding non-cisplatin based combination regimens, but there was insufficient evidence to make a specific recommendation.

Research recommendation	**In which people with muscle-invasive bladder cancer does neo-adjuvant chemotherapy improve outcomes?**
Why is this important	Level 1 evidence shows that neoadjuvant chemotherapy produces a significant survival benefit for people with muscle invasive bladder cancer. The majority of this benefit is thought to accrue in those who have a major (particularly complete response) to chemotherapy. A small proportion of people may progress during chemotherapy have a poorer prognosis and may suffer a survival detriment by delay of definitive treatment. If the outcome of chemotherapy could be predicted by a pre-treatment 'biomarker' (in this context a biomarker could be, for example, a specific biological profile or change or by a certain imaging characteristic) then neoadjuvant chemotherapy could be directed at those with most to gain from it and alternative strategies defined for those likely to respond poorly, avoiding unnecessary toxicity and treatment delays. This could result in an overall improvement of outcomes.

5.1.2 Adjuvant chemotherapy

Chemotherapy after radical treatment (adjuvant chemotherapy) is not commonly used but is usually confined to people who have had radical cystectomy but who have not had neoadjuvant chemotherapy. In these people it is considered when the pathology findings from the radical cystectomy show invasion into the deep layers of muscle or beyond, involvement of lymph nodes, lymphovascular invasion or variant pathology.

A practical problem is that these people with a poor prognosis may not be suitable for chemotherapy because their recovery from radical cystectomy may be prolonged or may have been complicated.

There is uncertainty about which patients should be offered adjuvant chemotherapy and which regimens are most effective.

Clinical question: Which patients with bladder cancer should be offered adjuvant chemotherapy?

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Clinical evidence (see also full evidence review)

The evidence is summarised in table 82.

Evidence statements

Overall survival

One systematic review and meta-analysis of nine randomised trials including 945 patients, reported a pooled hazard ratio (HR) for overall survival of 0.77 (95% CI 0.59 to 1.00) (Leow *et al.*, 2014). The addition of data from 284 patients from the EORTC trial (Sternberg *et al.*, 2014) provided a pooled HR of 0.77 (95% CI 0.62 to 0.96) in favour of adjuvant chemotherapy, equivalent to a 23% relative decrease in the risk of death with local treatment and adjuvant chemotherapy compared to local treatment alone (moderate quality evidence).

In an analysis of trials based on the type of chemotherapy used, the HR for one trial with only 45 events that used single-agent cisplatin was 1.02 (95% CI 0.57 to 1.84), suggesting uncertainty about the effect of adjuvant chemotherapy on overall survival. For the seven trials that used cisplatin-based combination chemotherapy, the pooled HR was 0.75 (95% CI 0.62 to 0.91), representing a 26% relative decrease in the risk of death on chemotherapy compared to that on control (moderate quality evidence). For two trials using gemcitabine-cisplatin combination chemotherapy the pooled HR was 0.71 (95% CI 0.21 to 2.35), with wide confidence intervals suggesting uncertainty about the effect of adjuvant chemotherapy on overall survival (low quality evidence).

Disease-free survival

A meta-analysis of nine trials including 1,106 patients provided an overall HR of 0.64 (95% CI 0.49 to 0.85), representing a 36% relative decrease in the risk of recurrence or death on chemotherapy compared to that on control. However, a moderate amount of between-trial heterogeneity or inconsistency was identified between the trials ($p=0.007$; $I^2=62\%$) (low quality evidence). For the six trials (690 patients) that used cisplatin-based combination chemotherapy the HR was 0.60 (95% CI 0.47 to 0.75), representing a 40% relative decrease in the risk of recurrence or death on chemotherapy compared to that on control (moderate quality evidence).

Metastases-free survival

Low quality evidence from the Advanced Bladder Cancer (ABC, 2006) meta-analysis reported that only two trials of 192 patients with 115 events provided data for metastases-free survival. This analysis was therefore extremely limited due to the low number of patients and was not presented.

Treatment-related morbidity

Treatment-related morbidity was not reported in the existing meta-analyses. Cognetti *et al.* (2012) provided low quality evidence on toxicities resulting from adjuvant gemcitabine and cisplatin therapy. Out of the 89 patients who received adjuvant chemotherapy 28.1% experienced grade three or four neutropenia, 14.6% experienced grade three or four thrombocytopenia, and 12.4% experienced grade three or four leukopenia. These were the most common toxicities reported. In the trial by Lehmann *et al.* (2006), three patients in the MVAC/MVEC chemotherapy arm had severe and recurrent vomiting. None of the patients had loss of renal function.

Treatment-related mortality

Treatment-related mortality was not reported in the existing meta-analyses. Cognetti *et al.* (2012) reported that there were no drug toxicity-related deaths. There was one death due to

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treatment toxicity in the immediate adjuvant chemotherapy arm in one trial (Sternberg *et al.*, 2014).

Health-related quality of life

Quality of life was not reported in the existing meta-analyses. Cognetti *et al.* (2012) provided low quality evidence that global quality of life was similar for patients in both arms of the trial. In the adjuvant chemotherapy arm there was a slight worsening of general quality of life during the last two months of chemotherapy, which improved during follow-up and was then comparable to the control group (number of patients and mean values not reported).

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Table 82: GRADE evidence profile: Which patients with bladder cancer should be offered adjuvant chemotherapy? ComparisonL Adjuvant chemotherapy + radical treatment verses radical treatment alone (or deferred chemotherapy)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant CT + local treatment	local treatment alone	Relative (95% CI)	Absolute	Quality
Overall survival											
10[1]	randomised trials	serious[2]	none	none	none	none	287/616 (46.6%)	346/613 (56.4%)	HR 0.77 (0.62 to 96)	92 fewer per 1000 (from 15 fewer to 162 fewer)	MODERATE
Overall survival - Single agent Cisplatin											
1[1]	randomised trials	serious[2]	none	none	serious[3,4]	none	23/46 (50%)	22/45 (48.9%)	HR 1.02 (0.57 to 1.84)	7 more per 1000 (from 171 fewer to 220 more)	LOW
Overall survival - Cisplatin-based combination											
7[1]	randomised trials	serious[2]	none	none	none	none	194/400 (48.5%)	241/402 (60%)	HR 0.75 (0.62 to 0.91)	103 fewer per 1000 (from 34 fewer to 167 fewer)	MODERATE
Overall survival - Gemcitabine-Cisplatin combinations											
2[1]	randomised trials	serious[2]	serious[5]	none	serious[3,4]	none	70/170 (41.2%)	83/166 (50%)	HR 0.71 (0.21 to 2.33)	111 fewer per 1000 (from 365 fewer to 301 more)	VERY LOW
Disease-free survival											
8[1]	randomised trials	serious[2]	serious[5]	none	None	none	270/555 (48.6%)	337/551 (61.2%)	HR 0.64 (0.49 to 0.85)	158 fewer per 1000 (from 59 fewer to 241 fewer)	LOW
Disease-free survival - Single agent Cisplatin											
1[1]	randomised trials	serious[2]	None	none	serious[3,4]	none	24/46 (52.2%)	23/45 (51.1%)	HR 1.02 (0.58 to 1.8)	7 more per 1000 (from 171 fewer to 213 more)	LOW
Disease-free survival - Cisplatin based combination											
6[1]	randomised trials	serious[2]	None	none	None	none	173/344 (50.3%)	220/346 (63.6%)	HR 0.60 (0.47 to 0.75)	181 fewer per 1000 (from 258 fewer to 364 fewer)	MODERATE
Disease-free survival - Gemcitabine-Cisplatin combinations											
2[1]	randomised	serious[2]	serious[5]	none	serious[3,4]	none	73/165	94/160	HR 0.64	155 fewer per	LOW

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adjuvant CT + local treatment**	**local treatment alone**	**Relative (95% CI)**	**Absolute**	**Quality**
	trials						(44.2%)	(58.8%)	(0.23 to 1.79)	1000 (from 403 fewer to 208 more)	
Metastases-free survival											
2[6]	randomised trials						115/192				
Grade 3-4 Thrombocytopenia (assessed with: WHO grading system)											
1[7]	randomised trials	serious[8]	None	none	serious[4]	none	13/89 (14.6%)	-	-	-	LOW
Grade 3-4 Neutropenia (assessed with: WHO grading system)											
1[7]	randomised trials	serious[8]	None	none	serious[4]	none	25/89 (28.1%)	-	-	-	LOW
Grade 3-4 Leukopenia (assessed with: WHO grading system)											
1[7]	randomised trials	serious[8]	None	none	serious[4]	none	11/89 (12.4%)	-	-	-	LOW
Severe vomiting											
1[9]	randomised trials	serious[10]	None	none	serious[4]	none	3/21 (14.3%)	-	-	-	LOW
Treatment-related mortality											
2[11]	randomised trials	serious[8]	None	none	serious[4]	none	1/230 (0.4%)	-	-	-	LOW
Health related quality of life											
1[7]	randomised trials	serious[8,12]	None	none	serious[4]	none	-	-	-	Values not reported. QoL similar in both arms.	LOW

[1] As reported in systematic review by Leow et al (2014) and the addition of data from Sternberg et al. (2014) [2] All trials were non double-blinded or open-label trials. Individual patient data not available for 3 trials. Many studies closed early due to poor accrual or low benefit. In two trials (Lehmann et al. 2006) around 25% of patients randomised to chemotherapy did not receive it; many received no therapy at all or received regimens other than in the trial protocol. Four trials (Lehmann, et al. 2006) did not specify salvage chemotherapy for patients on the control arm whose disease progressed or recurred. For Sternberg et al. (2014) only a conference abstract was available so study quality could not be assessed. The HR for progression-free survival was calculated from number of events and p value assuming randomisation ratio of 1:1 [3] Wide confidence interval (includes null effect) limits the precision of this outcome [4] Low number of events limits precision of outcome [5] Significant statistical heterogeneity present. [6] As reported in Cochrane meta-analysis (ABC, 2006) - Data on metastases-free survival were only available for 2 trials including 192 patients and 115 events and were therefore not presented in the Cochrane meta-analysis [7] Cognetti et al. (2012) [8] Non-blinded study. Study closed early for low accrual. IPD not available. [9] Lehmann et al. (2006) [10] No blinding reported. Trial stopped early for benefit. [11] Cognetti et al. (2012); Sternberg et al. (2014) [12] Mean QoL values and number of respondents not reported

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider adjuvant cisplatin combination chemotherapy after radical cystectomy for people with a diagnosis of muscle-invasive or lymph-node-positive urothelial bladder cancer for whom neoadjuvant chemotherapy was not suitable (because muscle invasion was not shown on biopsies before cystectomy). Ensure that the person has an opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer.**
Relative value placed on the outcomes considered	All outcomes from the PICO were considered important by the GDG. Overall survival and disease-free survival are the most reliable and important indicators of clinical benefit. Quality of life is important for the patient. No additional outcomes were used by the GDG to make recommendations.
Quality of the evidence	The quality of the evidence was low to moderate as assessed with GRADE. The evidence was limited by the outdated regimens that were used in the trials and there have since been improvements in radical therapy. However, because there have been improvements in radical therapy since most of the trials were published, modern regimens are at least as effective as those used in the trials. The benefits reported in the evidence should be seen as the minimum gain that modern day patients should expect. There was heterogeneity in the meta-analysis and most trials had small patient numbers. Potential biases were highlighted in several studies as the trials closed prematurely. These issues and the quality of the evidence affected the strength of the recommendation that could be made. The GDG also considered the evidence on neoadjuvant chemotherapy . There was moderate quality evidence of improved survival with adjuvant cisplatin-based chemotherapy, so the GDG felt that there was enough evidence to make a ‘consider’ recommendation. The strong recommendation for neoadjuvant chemotherapy made in section 5.1.1 should ensure that all suitable patients receive neoadjuvant chemotherapy. However, the above recommendation was made because the GDG wanted to ensure that if neoadjuvant chemotherapy was not given, because muscle invasion was not shown on biopsies before cystectomy, that patients would receive adjuvant chemotherapy. No research recommendation was made. The GDG considered making a research recommendation but were aware of an adjuvant chemotherapy trial that closed early due to poor recruitment. It is possible that patients in this category could be included in the research recommendation made in section 5.1.1.
Trade-off between clinical benefits and	The GDG weighed up the clinical benefits of improved clinical outcomes in patients with MIBC who are suitable for cisplatin-based chemotherapy

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harms	against the harm of the toxicity of additional chemotherapy. The GDG considered that increased survival outweighs short-term toxicity.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG considered the potential costs of the recommendation arise from the chemotherapy delivery and management of toxicity. There may also be an increase in post-cystectomy oncology review. The potential savings include cessation of best supportive care. The GDG agreed that improved survival is likely to be cost-effective. The GDG considered that the QALY gain is likely to be sufficient to make the recommendation cost-effective
Other considerations	The GDG considered that there are no equalities issues as the recommendations would still consider those with hearing impairments for adjuvant chemotherapy. The GDG was unsure of the extent of change in practice required to implement the recommendation but acknowledged that there is likely to be an increase in the use of adjuvant chemotherapy. Consideration was given to patient choice. The GDG felt strongly that the focus should be on neoadjuvant chemotherapy and that adjuvant chemotherapy is not a suitable alternative. They recognised that there may be patients who are not eligible for neoadjuvant chemotherapy who may still benefit from adjuvant treatment.

5.2 Treatment of organ confined muscle-invasive bladder cancer

5.2.1 Radical cystectomy versus radical radiotherapy

In people with muscle invasive bladder cancer, either radical radiotherapy or radical cystectomy are almost always advised.

Radical cystectomy is major abdominal surgery with a long hospital stay, a high risk of post operative complication and long post operative recovery. Life changing consequences include a urostomy for many patients, a profound impact on sexual function and associated psychological consequences. Radical radiotherapy involves daily treatment over 4-6 weeks, and is associated with side effects including effects on bladder and bowel function, general debilitation and adverse impact on sexual function. In many countries at present, including the UK, there is a view that the chance of cure may be higher with radical cystectomy than radical radiotherapy, and this is the justification for the common recommendation of radical cystectomy rather than radical radiotherapy, despite the greater adverse impact of radical cystectomy on quality of life.

There are patient related factors that may affect the suitability of radical cystectomy or radical radiotherapy for them. Radical cystectomy may not be suitable for those who are frail or elderly, those who have other serious medical conditions, or those who do not have sufficient mental capacity to be able to participate actively in recovery from radical cystectomy. Radical radiotherapy may not be suitable for people who have had previous pelvic radiotherapy, who have certain bowel disorders (inflammatory bowel disease), who have had significant previous pelvic surgery (that might result in adhesions with bowel stuck to the bladder), or who have obstruction to one or both kidneys, or who have carcinoma in situ.

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Given that the treatments differ so much in terms of their impact, it is crucial to identify those patients who would have better outcomes with surgery than with radical radiotherapy, and vice versa.

Clinical question: In which patient groups with muscle invasive bladder cancer would radical cystectomy produce better outcomes than radical radiotherapy and in which groups would radical radiotherapy produce better outcomes?

Clinical evidence (see also full evidence review)

The evidence is summarised in tables 83 to 86.

Evidence statements

Low quality evidence from one systematic review of three randomised trials (439 patients) suggests that pre-operative radiotherapy followed by radical cystectomy (surgery) more effective than radical radiotherapy with salvage cystectomy (radiotherapy) in terms of overall survival at three years (OR 1.91, 95% CI 1.30 to 2.87) and at five years (OR 1.87, 95% CI 1.22 to 2.87). Overall survival at three years was 45% for surgery and 28% for radiotherapy, giving an absolute improvement of 16%. One trial reported low quality evidence of disease-specific survival with an odds ratio in favour of surgery but this was not statistically significant at three years (OR 1.66, 95% CI 0.92 to 2.99) or five years (OR 1.39, 95% CI 0.75 to 2.57) (Shelley et al., 2001).

Six comparative observational studies (4,328 patients) provided very low quality evidence about overall survival at five years, which ranged from 37% to 53% across studies for cystectomy and from 21% to 68% for radiotherapy (Munro et al., 2010; Gore et al., 2010; Bekelman et al., 2012; Kotwal et al., 2008; van der Steen-Banasik et al., 2009; Koga et al., 2009). Five out of the six studies reported no significant difference between treatments in terms of overall survival. One study of 10,807 patients provided low quality evidence suggesting an overall survival advantage for those who had radical cystectomy compared to bladder preserving therapy (including radiotherapy) in all age groups (Chamie et al., 2008). The survival benefit was smaller for patients over 79 years old (18 months versus 15 months) although the 95% confidence intervals still suggest a significant difference in favour of surgery (HR 1.32, 95% 1.19 to 1.46). In four series of bladder trimodality therapy (TURBT + chemoradiotherapy) five-year overall survival ranged from 51% to 68%, which compares to 58% in one large cystectomy series of 1100 patients (Mak et al., 2012; Shipley et al., 2002; Rodel et al., 2002; Perdona et al., 2008).

Five comparative observational studies reported very low quality evidence of five-year disease-specific survival, with none of the studies reporting a significant difference between radical cystectomy (53% to 67%) and radiotherapy (48% to 75%) (Gore et al., 2010; Bekelman et al., 2012; Kotwal et al., 2008; van der Steen-Banasik et al., 2009; Koga et al., 2009). In three large cystectomy series, five-year disease-specific survival ranged from 65% to 76% (Rink et al., 2012; Hautmann et al., 2012; Otto et al., 2012). One study of 10,807 patients provided low quality evidence suggesting an advantage in disease-specific survival for those who had radical cystectomy compared to bladder preserving therapy (including radiotherapy) in all age groups (Chamie et al., 2008).

One study of 141 patients with T2N0M0 bladder cancer provided very low quality evidence about adverse events after cystectomy or brachytherapy (van der Steen-Banasik et al., 2009). Acute toxicity (<3 months) after cystectomy was seen in 34 patients (52%), including sepsis, UTI, and wound problems. Late toxicity was seen in 30 patients (46%) after cystectomy, including stoma problems and ureter/ureter anastomosis problems. In the brachytherapy group, acute toxicity was observed in 13 patients (17%), with six patients developing wound infections. Eight cases of late toxicity were observed, including five cases of fistula requiring a temporary suprapubic catheter.

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In one observational study 19% (57/302) of patients received subsequent salvage cystectomy after primary radical radiotherapy (Munro et al., 2010). Similarly, in three trimodality therapy series bladder preservation rates in long-term survivors ranged from 80% to 83% (Shipley et al., 2002; Rodel et al., 2002; Perdona et al., 2008).

Quality of life was reported by one observational study of 58 patients after radical radiotherapy and 251 patients after radical cystectomy (Henningsohn et al., 2002). Distress from bowel function was reported in 24% of cystectomy patients and 32% of radiotherapy patients (RR 0.74, 95% CI 0.45 to 1.21). Factors related to sexual dysfunction were lower after radiotherapy than after cystectomy.

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Table 83: GRADE evidence profile: In which patient groups with muscle invasive bladder cancer would radical cystectomy versus radical radiotherapy produce better outcomes (randomised trials)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	Radiotherapy	Relative (95% CI)	Absolute	Quality
Overall survival at 3 yrs: intent-to-treat analysis											
3[1]	randomised trials	none	none	serious[2]	serious[3]	none	97/221 (43.9%)	63/218 (28.9%)	OR 1.93 (1.3 to 2.87)	151 more per 1000 (from 57 more to 249 more)	LOW
Overall survival at 5 yrs: intent-to-treat analysis											
3[1]	randomised trials	none	none	serious[2]	serious[3]	none	74/221 (33.5%)	46/218 (21.1%)	OR 1.87 (1.22 to 2.87)	122 more per 1000 (from 35 more to 223 more)	LOW
Overall survival at 3 yrs: treatment received analysis											
2[1]	randomised trials	none	none	serious[2]	serious[3]	none	67/143 (46.9%)	56/173 (32.4%)	OR 1.86 (1.17 to 2.94)	147 more per 1000 (from 35 more to 261 more)	LOW
Overall survival at 5 yrs: treatment received analysis											
3[1]	randomised trials	none	none	serious[2]	serious[3]	none	66/173 (38.2%)	45/205 (22%)	OR 2.17 (1.39 to 3.41)	159 more per 1000 (from 62 more to 270 more)	LOW
Disease-specific survival at 3 yrs: intent-to-treat analysis											
1[1]	randomised trials	none	none	serious[2]	serious[3,4]	none	44/98 (44.9%)	30/91 (33%)	OR 1.66 (0.92 to 2.99)	120 more per 1000 (from 18 fewer to 266 more)	LOW
Disease-specific survival at 5 yrs: intent-to-treat analysis											
1[2]	randomised trials	none	none	serious[2]	serious[3,4]	none	35/98 (35.7%)	26/91 (28.6%)	OR 1.39 (0.75 to 2.57)	72 more per 1000 (from 55 fewer to 221 more)	LOW
Disease-specific survival at 10 yrs: intent-to-treat analysis											
1[1]	randomised trials	none	none	serious[2]	serious[3,4]	none	30/98 (30.6%)	18/91 (19.8%)	OR 1.79 (0.91 to 3.5)	108 more per 1000 (from 15 fewer to 265 more)	LOW
Disease-specific survival at 3yrs: treatment received analysis											
1[1]	randomised trials	none	none	serious[2]	serious[3]	none	41/77 (53.2%)	31/85 (36.5%)	OR 1.98 (1.06 to 3.72)	167 more per 1000 (from 14 more to 316 more)	LOW
Disease-specific survival at 5 yrs: treatment received analysis											
1[1]	randomised trials	none	none	serious[2]	serious[3,4]	none	34/77 (44.2%)	26/85 (30.6%)	OR 1.79 (0.94 to 3.42)	135 more per 1000 (from 13 fewer to 295 more)	LOW

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery**	**Radiotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**
Complication rate											
1[1]	randomised trials	none	none	serious[2]	serious[3]	none	60/125 (48%)	75/533 (14.1%)	-	-	LOW
Late rectal complications											
1	randomised trials	none	none	serious[2]	serious[3,5]	none	36%	30%	-	-	LOW
Health-related quality of life											
0	No evidence available										
Subsequent treatment											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										

[1] Data from systematic review by Shelley et al. (2001) [2] No randomised trials comparing surgery alone with radiotherapy alone. 3 trials compared preoperative RT followed by cystectomy versus radical RT with salvage cystectomy. Treatment may not be relevant to current practice. [3] Low number of events limits precision [4] Confidence interval includes null value [5] Number of events and patients not reported

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Table 84: GRADE evidence profile: In which patient groups with muscle invasive bladder cancer would radical cystectomy versus radical radiotherapy produce better outcomes (comparative observational studies)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cystectomy	Radiotherapy	Relative (95% CI)	Absolute	Quality
Overall mortality rate (follow-up median 36-42 months)											
2[1]	observational studies	None	none	none	serious[2]	none	42/103 (40.8%)	39/132 (29.5%)	RR 1.42 (1 to 2.02)	124 more per 1000 (from 0 more to 301 more)	VERY LOW
Overall survival at 3 yrs (follow-up mean 34 months)											
1[3]	observational studies	none	none	none	serious[2]	none	69%	39%	-	Favours surgery (p=0.03)	VERY LOW
Overall survival at 5 yrs											
6[4]	observational studies	none	serious[5]	none	None	none	Range 37% - 53%	Range 21% - 68%	-	5/6 studies showed no difference between treatments	VERY LOW
Overall survival (median OS in patients aged <60 yrs)											
1[6]	observational studies	none	None	none	None	none	1783	214	HR 1.64 (1.34-1.99)	Median OS 74mo after RC vs. 28mo after RT	LOW
Overall survival (median OS in patients aged 60-69 yrs)											
1[6]	observational studies	none	None	none	None	none	2474	401	HR 1.54 (1.34-1.76)	Median OS 49mo after RC vs. 24mo after RT	LOW
Overall survival (median OS in patients aged 70-79yrs)											
1[6]	observational studies	none	None	none	None	none	2873	931	HR 1.52 (1.38-1.66)	Median OS 33mo after RC vs. 19mo after RT	LOW
Overall survival (median OS in patients aged >79yrs)											
1[6]	observational studies	none	None	none	None	none	904	1227	HR 1.32 (1.19-1.46)	Median OS 18mo after RC vs. 15mo after RT	LOW
Progression-free survival at 3yrs											
1[7]	observational studies	none	None	none	serious[2]	none	72.5%	69%	-	Uncertainty of a difference between treatments	VERY LOW
Disease-specific survival at 5 yrs											
5[8]	observational studies	none	serious[5]	none	None	none	Range 53%-67%	Range 48%-75%	-	None of the studies reported a significant difference	VERY LOW
Disease-specific survival (median DSS in patients aged<60yrs)											
1[6]	observational	none	None	none	None	none	1783	214	HR 1.69	Median DSS not	LOW

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Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cystectomy	Radiotherapy	Relative (95% CI)	Absolute	Quality
	studies								(1.35-2.11)	reached after RC vs. 43mo after RT	
Disease-specific survival (median DSS in patients aged 60-69 yrs)											
1[6]	observational studies	none	None	none	None	none	2474	401	HR 1.55 (1.32-1.83)	Median DSS 141mo after RC vs. 42mo after RT	LOW
Disease-specific survival (median DSS in patients aged 70-79 yrs)											
1[6]	observational studies	none	None	none	None	none	2873	931	HR 1.31 (1.16-1.48)	Median DSS 132mo after RC vs. 40mo after RT	LOW
Disease-specific survival (median DSS in patients aged >79 yrs)											
1[6]	observational studies	none	None	none	None	none	904	1227	HR 1.21 (1.07-1.38)	Median DSS 37mo after RC vs. 22mo after RT	LOW
Distant recurrence rate (follow-up median 82 months)											
1[9]	observational studies	none	None	none	serious[2]	none	27/72 (37.5%)	33/97 (34%)	RR 1.10 (0.73 to 1.66)	34 more per 1000 (from 92 fewer to 225 more)	VERY LOW
5 yr distant recurrence rate – subgroup cT2 only (follow-up median 46 months)											
1[10]	observational studies	none	None	none	serious[2]	none	9%	12%	-	Uncertainty of a difference between treatments (p=0.4)	VERY LOW
5 yr distant recurrence rate – subgroup cT3 only (follow-up median 46 months)											
1[10]	observational studies	none	None	none	serious[2]	none	62%	31%	-	Favours LCRT but non-significant (p=0.09)	VERY LOW
Treatment-related morbidity: acute toxicity											
1[11]	observational studies	none	None	none	serious[2]	none	34/65 (52.3%)	13/75 (17.3%)	RR 3.02 (1.75 to 5.21)	350 more per 1000 (from 130 more to 730 more)	VERY LOW
Treatment-related morbidity: Late toxicity											
1[11]	observational studies	none	None	none	serious[2]	none	30/65 (46.2%)	-	-	-	VERY LOW
Treatment-related mortality (assessed with: 3-month mortality rate)											
1[12]	observational studies	none	None	none	serious[2]	none	8/96 (8.3%)	5/302 (1.7%)	RR 5.03 (1.69 to 15.02)	67 more per 1000 (from 11 more to 232 more)	VERY LOW
Health-related quality of life (assessed with: Distress from bowel function)											
1[13]	observational	none	None	none	serious[2]	none	39/166	15/47	RR 0.74	83 fewer per 1000	VERY

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cystectomy**	**Radiotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**
	studies						(23.5%)	(31.9%)	(0.45 to 1.21)	(from 176 fewer to 67 more)	LOW
Health-related quality of life (assessed with: Dissatisfaction with sexual function (males only))											
1[13]	observational studies	none	None	none	serious[2]	none	67%	36%	RR 0.6 (0.4 to 1.0)	Favours RT	VERY LOW
Health-related quality of life (assessed with: Erectile dysfunction)											
1[13]	observational studies	none	none	none	serious[2]	none	92%	75%	HR 0.8 (0.6 to 1.0)	Favours RT	VERY LOW
Subsequent treatment (assessed with: salvage cystectomy in RT group)											
1[12]	observational studies	none	none	none	serious[2]	none	-	57/302 (18.9%)	-	-	VERY LOW

[1] Koga et al. (2009): Low-dose chemo-radiation followed by partial or radical cystectomy versus immediate cystectomy; Haresh et al. (2007): Chemo-radiation versus radical cystectomy [2] Low number of events limits precision [3] Kalogeras et al. (2008) [4] Chahal et al. 2003/Munro et al. 2010; Gore et al. 2010; Bekelman 2012; Kotwal et al. 2008; van der Steen-Banasik 2009; Koga et al. 2009 [5] Treatment regimes and length of follow-up varied across studies. Number of events not reported. [6] Chamie et al. 2008 [7] Mayans et al. (2010): Chemoradiation versus radical cystectomy [8] Gore et al. 2010; Bekelman 2012; Kotwal et al. 2008; van der Steen-Banasik 2009; Koga et al. 2008 [9] Kotwal et al. 2008: Cystectomy vs radical radiotherapy (no concurrent chemo) [10] Koga et al. 2009 [11] van der Steen-Banasik 2009 [12] Chahal et al. 2003 [13] Henningsohn et al. 2002

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Table 85: GRADE evidence profile: In which patients with bladder cancer would trimodality therapy produce better outcomes (non-comparative series)

Quality assessment							No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trimodality therapy	Relative (95% CI)	Absolute	Quality
Overall survival at 5 years										
4[1]	observational studies	None	none	none	none	None	N=1194 Range 51%-68%	n/a	n/a	LOW
5-year overall survival with bladder preservation										
3[2]	observational studies	none	none	none	none	None	N=726 Range 80%-83%	n/a	n/a	LOW
Local recurrence rate										
3[2]	observational studies	none	none	none	none	None	N=726 Range 34%-40%	n/a	n/a	LOW

[1]Mak et al. 2012; Shipley et al. 2002; Rodel et al. 2002; Perdona et al. 2008 [2] Shipley et al. 2002; Rodel et al. 2002; Perdona et al. 2008

Table 86: GRADE evidence profile: In which patients with bladder cancer would radical cystectomy produce better outcomes (non-comparative series)

Quality assessment							No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radical cystectomy	Relative (95% CI)	Absolute	Quality
Overall survival at 5 years										
1[1]	observational studies	none	none	none	none	None	N=1100 58%	n/a	n/a	LOW
Recurrence-free survival at 5 years										
2[2]	observational studies	none	none	none	none	None	N=4108 70%	n/a	n/a	LOW
Disease-specific survival at 5 years										
3[3]	observational studies	none	none	none	none	None	N=6591 Range 65%-76%	n/a	n/a	LOW

[1] Hautmann et al. 2012 [2] Rink et al. 2012; Hautmann et al. 2012 3 Rink et al. 2012; Hautmann et al. 2012; Otto et al. 2012

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Ensure that a specialist urology multidisciplinary team reviews all cases of muscle-invasive bladder cancer, including adenocarcinoma, squamous cell carcinoma and neuroendocrine carcinoma, and that the review includes histopathology, imaging and discussion of treatment options.** **Offer a choice of radical cystectomy or radiotherapy with a radiosensitiser to people with muscle-invasive urothelial bladder cancer for whom radical therapy is suitable. Ensure that the choice is based on a full discussion between the person and a urologist who performs radical cystectomy, a clinical oncologist and a clinical nurse specialist. Include in the discussion:** • **the prognosis with or without treatment** • **the limited evidence about whether surgery or radiotherapy with a radiosensitiser is the most effective cancer treatment** • **the benefits and risks of surgery and radiotherapy with a radiosensitiser, including the impact on sexual and bowel function and the risk of death as a result of the treatment.**
Relative value placed on the outcomes considered	The GDG considered all outcomes to be important except for subsequent treatment. Survival was considered an important outcome for patients and quality of life as important for survivorship. Subsequent treatment was not considered an important outcome because the GDG felt that in this situation survival and quality of life outweighed issues regarding subsequent treatment. All outcomes from the PICO were reported in the evidence and no additional outcomes were used by the GDG to make recommendations.
Quality of the evidence	The quality of the evidence was very low to low as assessed with GRADE. The main limitation of the evidence was that no relevant contemporary randomised studies were identified. The non-comparative studies were considered to be of limited use due to potential for bias which included patient selection for treatments, retrospective design, stage migration, and non comparable groups. These limitations meant that the GDG could not recommend one treatment over the other, so the GDG made the recommendation to discuss the risks and benefits of both treatments with the patient within a SMDT. The recommendation that patients should have some treatment rather than no treatment at all was based on clinical consensus, because survival for these patients without any treatment is very poor.

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	Discussion with cystectomist and oncologist was based on the existing urological cancer IOG and consensus within the GDG. No research recommendation was made to compare surgery and radiotherapy because a randomised trial has been attempted in the UK but it was unfeasible due to clinician and patient bias. The GDG did make a research recommendation to assess if selecting treatment using biomarkers is an effective strategy because it is unclear which groups of patients will benefit from surgery or radiotherapy. Research into quality of life was recommended as little is known about quality of life in these patients.
Trade-off between clinical benefits and harms	The potential benefits of the recommendations include more informed patient decision-making and patient support, improved equality of access to both treatment options, improved MDT working and improved cancer outcomes for patients. The GDG considered that a potential harm of the recommendations is that some patients may find decision-making stressful. The GDG agreed that offering treatment choice to every patient was very important. The GDG agreed that giving this opportunity to all patients was of greater benefit than of giving too much information to some patients.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG considered the potential costs of the recommendation to be from increased specialist consultations/ SMDT discussion, and increased treatment costs. The extent of these costs is unknown. The potential savings included reduced costs of best supportive care/palliative treatment.
Other considerations	The GDG considered that these recommendations will be beneficial because older patients and/or those with significant co-morbidities, or those with disabilities who still need a discussion will be considered. The GDG considered it important that all clinicians should give patients a choice of treatment for MIBC. Increased centralisation of specialist services and improved access to CNS support will be required. The GDG acknowledged that it is difficult to know how much of a change in practice this will require and may vary across the country.

Research recommendation	**In patients with muscle-invasive bladder cancer suitable for radical treatment, does the use of biomarkers enable patients to select more effective treatment, and improve their outcomes compared with treatment selected without biomarkers?**
Why is this important	Response to surgery or radiotherapy is difficult to predict for individuals. There is variation not only in the cure rates for patients with muscle-invasive bladder cancer treated with either surgery or radiotherapy, but also in the side effects experienced during and after treatment. The usefulness of current biomarkers in predicting treatment outcomes for individual patients has not been clearly established. Currently treatment decisions are based on patient-related factors, and patient and clinician preference. Research into biomarkers that can predict the response of

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	the patient's muscle-invasive bladder cancer to either radiotherapy or surgery could help individual patients and clinicians decide which treatment is more suitable and is considered an important step toward individualised treatment.

Research recommendation	**What is the quality of life (and other patient-reported outcomes) of patients with muscle-invasive bladder cancer before, during and after radical treatment?**
Why is this important	Very little is known about quality of life and other patient reported outcomes for bladder cancer patients with muscle-invasive bladder cancer during the course of their diagnosis and treatment and after treatment. From the National Patient Experience Survey we know that urological cancer patients other than prostate cancer have a worse experience then prostate cancer patients. Many of these patients will have been treated for bladder cancer. The potential physical and psycho-social side effects following radical treatment for bladder cancer are known but their prevalence and impact on patients' lives are not. Moreover, it is important to know whether radical treatment has different impacts on patient sub-groups for example females and males, younger and older patients.

5.2.2 Optimal radical radiotherapy regimen

5 year survival rates of around 50% can be achieved for people with muscle-invasive bladder cancer using external beam radiotherapy or surgery. Within the UK, there are two commonly used radiotherapy schedules to treat bladder cancer. These are 52.5-55 Gy in 20 fractions over 4 weeks and 64Gy in 32 fractions over 6.5 weeks. The two schedules have never been directly compared and to date, radiotherapy trials in the UK have included both regimes. Treatment side-effects and disease-outcome are considered to be comparable between the two protocols.

Although many UK centres now treat potentially curative patients with radical radiotherapy and a radiosensitiser, there are a group of patients who are not fit or able to tolerate radiosensitisation. These patients are treated with radical radiotherapy alone as their definitive treatment.

There are differences of opinion about the volume of tissue to be treated, the radical radiotherapy regimens to be used and the use of radiosensitisers.

Clinical question: What is the optimal radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer?

Clinical evidence (see also full evidence review)

The evidence is summarised in tables 87 to 95.

Evidence statements

Radiotherapy with carbogen and nicotinamide (RT+CON) versus radiotherapy alone

Moderate quality evidence from one randomised trial (Hoskin, *et al.*, 2009; 2010) of 333 participants suggests that there is a 13% improvement in three-year overall survival from 46% to 59% in favour of RT+CON compared to radiotherapy alone (HR 0.85, 95% CI 0.73 to 0.99). There was an 11% increase in relapse-free survival at three years in favour of RT+CON (43% vs 54%), although the confidence interval of the hazard ratio includes the null value, suggesting uncertainty about the difference between groups (HR 0.86, 95% CI 0.74 to

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1.00). Rates of urinary (39% and 32%) and GI (7% and 5%) complications were similar between groups. Larger doses per fraction did not increase bladder or bowel morbidity. Two deaths (1.2%) were considered due to RT+CON and one death (0.6%) to radiotherapy alone.

Chemoradiotherapy (CRT) with 5-fluorouacil and mitomycin C versus radiotherapy alone

Moderate quality evidence from one randomised trial (James *et al.*, 2012) of 360 participants suggests that loco-regional disease free survival is better with chemoradiotherapy (mitomycin C and 5-fluorouacil) compared to radiotherapy alone, with two-year recurrence free rates of 67% versus 54% (HR 0.68, 95% CI 0.48 to 0.96). The chemoradiotherapy effect did not vary significantly between radiotherapy type or dose fractionation or with neoadjuvant chemotherapy. Overall there were 98 deaths in the chemoradiotherapy group and 110 in the radiotherapy group, with an absolute difference in five-year survival of 7% (95% CI, -3% to 17%) in favour of chemoradiotherapy, although the confidence interval of the hazard ratio includes the null value, suggesting uncertainty of a difference between groups (HR 0.82, 95% CI 0.63 to 1.09). There was also uncertainty about the relative effectiveness in terms of disease-specific survival (HR 0.77, 95% CI 0.57 to 1.05) and disease-free survival (0.78, 95% CI 0.6 to 1.03). Metastases-free survival was better in the chemoradiotherapy group, with an improvement of 11.3% (0.4% to 21.1%) at five years (HR 0.72, 95% CI 0.53 to 0.99). Acute grade three or four toxic effects were increased in the chemoradiotherapy groups compared to radiotherapy alone (36% vs 27.5%), although the risk ratio includes the null value suggesting uncertainty of a difference between groups (RR 1.31, 95% CI 0.96 to 1.78). Grade three or four RTOG late events occurred at some point during follow-up in 8.3% (10/120) of the chemoradiotherapy group and 15.7% (17/108) of the radiotherapy group (RR 0.53, 95% CI 0.25 to 1.11). Very low quality evidence from one observational study of 50 patients treated with chemoradiotherapy (cisplatin and 5-fluorouracil) reports that mean scores for global quality of life and subscales were slightly improved six months after treatment and were maintained at over 70% (best quality of life score is 100%) for all patients alive without relapse.

Moderate quality evidence from the BC2001 trial reported in Huddart *et al.* (2013) suggest that rates of late side-effects were not significantly different between patients receiving reduced high-dose volume radiotherapy and standard whole-bladder radiotherapy (OR 1.34, 95% CI 1.42 to 4.28). The effect estimates for time to locoregional recurrence (HR 0.80, 95% CI 0.51 to 1.26) and overall survival (HR 0.82, 95% 0.58 to 1.16) also suggest uncertainty of a difference between treatment groups.

Accelerated fractionation (AF) versus conventional fractionation (CF) radiotherapy

Moderate quality evidence from one randomised trial of 229 participants suggests that there was no difference in relapse-free survival, overall survival, and local failure between accelerated fractionation (60.8Gy in 32 fractions over 26 days) and conventional fractionation (64Gy in 32 fractions over 45 days) (Horwich et al., 2005). At five years overall survival was 37% for AF and 40% for CF. There were two treatment related deaths, both on the AF arm. Acute grade two or three RTOG bowel toxicity was reported in 44% of AF patients compared to 26% of CF patients (RR 1.68, 95% CI 1.14 to 2.49). Late radiation toxicity was reported in 44% of the AF group and 35% of the CF group (RR 1.26, 95% CI 0.91 to 1.76).

Neoadjuvant MVC and RT versus concurrent cisplatin CRT

Very low quality evidence from one observational study reported that five-year overall survival was 73% for patients treated with either neoadjuvant chemotherapy and radiotherapy (n=41) or concurrent radiotherapy (n=39), with no difference between treatment protocols (Zapatero et al., 2012). There were also no differences between protocols for cancer-specific survival and distant metastases. Disease-free survival was improved with concurrent chemoradiotherapy compared to neoadjuvant chemotherapy (82% versus 67%). There were no differences in GI complications, although urinary toxicity was higher in the concurrent chemoradiotherapy group (33% versus 12%, RR 0.37, 95% CI 0.14 to 0.93).

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Neoadjuvant MVC + RT versus Neoadjuvant MVC + Concurrent platinum-based CRT

Very low quality evidence from one observational study suggests that five year overall survival (60% versus 72%, p=.008) and disease-specific survival (63% versus 79%, p=.003) are improved with neoadjuvant chemotherapy and concurrent chemoradiotherapy compared to neoadjuvant chemotherapy and radiotherapy alone (Perdona *et al.*, 2008). There were no significant differences between treatment protocols in terms of acute grade three or four bone marrow (16% overall), bladder (12% overall), or intestinal (12% overall) toxicity.

RT only versus Concurrent CRT

Very low quality evidence from one observational study reported on 473 patients with a median overall survival of 28.5 months in patients treated with RT compared to 70 months in those treated with concurrent chemoradiotherapy (Krause et al., 2011). One quality of life study including 48 long-term survivors after trimodality therapy reported that the mean physical functioning score was 89 (possible range 0-100) and the general health perceptions score was 74 (possible range 0-100) (Zietman et al., 2003). This suggests that global health-related quality of life is good in this population (very low quality evidence).

Conventional single-phase RT to whole bladder versus two-phase reduced volume treatment

One observational study (very low quality evidence) comparing conventional single phase radiotherapy with a two-phase technique limiting the high-dose area reported that median overall survival was 2.8 years with both techniques (HR 0.91, 95% CI 0.64 to 1.3) (Mangar et al., 2006). The two-phase treatment was associated with a lower rate of overall grade 3 to 4 late toxicity (44% versus 25%, RR 0.56, 95% CI 0.33 to 0.95), and fewer acute bladder and bowel toxicities.

Concomitant CRT with Gemcitabine versus RT alone

One very low quality study of 69 patients reported three year overall survival of 38% with concurrent chemoradiotherapy with gemcitabine and 27% with radiotherapy alone (Asadauskiene *et al.*, 2010). One quality of life study of 23 patients treated with concurrent gemcitabine and radiotherapy reported that there were no statistically significant changes in general quality of life scores before, during or after treatment (Herman *et al.*, 2004).

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Table 87: GRADE evidence profile: What is the optiam radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer? Comparison: Radiotherapy with carbogen and nicotinamide (RT+CON) versus radiotherapy alone

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT+CON	RT alone	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate; follow-up median 57-60 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	85/164 (51.8%)	100/163 (61.3%)	HR 0.85 (0.73 to 0.99)	3-yr OS 59% vs 46% in favour of RT+CON	MODERATE
Relapse-free survival (time to tumour recurrence in bladder (MIBC only), locoregional failure or death; follow-up median 57-60 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	N=164	N=163	HR 0.86 (0.74 to 1.00)	3-yr RFS 54% vs 43% in favour of RT+CON	MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	none	serious[2]	none	2/164 (1.2%)	1/163 (0.6%)	-	-	MODERATE
Grade 3 or worse urinary complications (assessed with: LENT/SOMA, 3yr incidence)											
1[1]	randomised trials	none	none	none	serious[2]	none	39%	32%	-	No significant difference (p=.4)	MODERATE
Grade 3 or worse GI complication (assessed with: LENT/SOMA, 3yr incidence)											
1[1]	randomised trials	none	none	none	serious[2]	none	7%	5%	-	No significant difference (p=.5)	MODERATE
Grade 1 or worse nausea/vomiting (assessed during first 7 weeks)											
1[1]	randomised trials	none	none	none	serious[2]	none	23-41%	6-12%	-	-	MODERATE
Health-related quality of life											
0	No evidence available										

[1] Hoskin et al. 2009/2010 (BCON trial) [2] Low number of events limits precision [3] Confidence interval includes null value

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Table 88: GRADE evidence profile: What is the optiam radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer? Comparison: Chemoradiotherapy (CRT) with 5-fluorouacil and mitomycin C versus radiotherapy alone

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT	RT	Relative (95% CI)	Absolute	Quality
Locoregional disease-free survival (rate of recurrence in pelvic nodes or bladder; follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	55/182 (30.2%)	76/178 (42.7%)	HR 0.68 (0.48 to 0.96)	2yr recurrence-free rate 67% vs 54% in favour of CRT	MODERATE
Invasive locoregional disease-free survival (follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	182	178	HR 0.57 (0.37 to 0.9)	2yr relapse rate 32% vs 18% in favour of CRT	MODERATE
Overall survival (any cause mortality rate; follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	98/182 (53.8%)	110/178 (61.8%)	HR 0.82 (0.63 to 1.09)	5yr OS rate 48% vs 35%, absolute difference 7% (-3 to 17%)	MODERATE
Disease-specific survival (mortality from bladder cancer; follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	74/182 (40.7%)	92/178 (51.7%)	HR 0.77 (0.57 to 1.05)	Uncertainty of difference between groups	MODERATE
Disease-free survival (follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	95/182 (52.2%)	113/178 (63.5%)	HR 0.78 (0.6 to 1.03)	Uncertainty of difference between groups	MODERATE
Metastasis-free survival (rate of metastasis; follow-up median 69.9 months)											
1[1]	randomised trials	none	none	none	serious[2]	none	71/182 (39%)	94/178 (52.8%)	HR 0.72 (0.53 to 0.99)	In favour of CRT	MODERATE
Grade 3-4 acute toxic effects (assessed with: NCI CTCAE during treatment)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	64/178 (36%)	50/182 (27.5%)	RR 1.31 (0.96 to 1.78)	85 more per 1000 (from 11 fewer to 214 more)	MODERATE
Grade 3-4 late RTOG events (assessed >6 months after randomisation)											
1	randomised trials	none	none	none	serious[2,3]	none	10/120 (8.3%)	17/108 (15.7%)	RR 0.53 (0.25 to 1.11)	74 fewer per 1000 (from 118 fewer to 17 more)	MODERATE
Grade 3-4 late LENT/SOMA toxicity (assessed >6 months after randomisation)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	29/77 (37.7%)	22/75 (29.3%)	RR 1.28 (0.82 to 2.02)	82 more per 1000 (from 53 fewer to 299 more)	MODERATE
Treatment-related mortality											
0	No evidence										

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CRT**	**RT**	**Relative (95% CI)**	**Absolute**	**Quality**
Health-related quality of life (EORTC QLQ-C30 in patients alive without cystectomy or disease; scale 0-100, higher scores are better)											
1[4]	observational study	none	none	none	serious[2]	none	N=505				VERY LOW

[1] James et al. 2012 (BC2001 trial); [2] Low number of events limits precision; [3] Confidence interval includes null value; [4] Lagrange et al. 2011; [5] Mean score for global QoL and for physical, emotional, personal, cognitive, and social functions were slightly improved 6 months after treatment and were maintained over 70% (scale 0% (worst) to 100% (best)) for all patients alive without relapse.

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Table 89: GRADE evidence profile: What is the optiam radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer? Comparison: Reduced high-dose volume versus standard volume radiotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Reduced high-dose volume**	**Standard volume**	**Relative (95% CI)**	**Absolute**	**Quality**
Locoregional recurrence-free survival (follow-up median 72.7 months; assessed with: recurrence in pelvic nodes or bladder)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	35/111 (31.5%)	41/108 (38%)	HR 0.80 (0.51 to 1.26)	2-year rate 64%vs 61%	MODERATE
Overall survival (follow-up median 72.7 months; assessed with: any cause mortality)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	62/111 (55.9%)	71/108 (65.7%)	HR 0.82 (0.58 to 1.16)	5-year survival 44% vs 38%	MODERATE
Grade 3/4 acute toxicity (assessed with: NCI CTCTAE during treatment)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	19/95 (20%)	30/120 (25%)	OR 0.79 (0.33 to 1.87)	42 fewer per 1000 (from 151 fewer to 134 more)	MODERATE
Any Grade 3/4 RTOG toxicity at any time during follow-up											
1[1]	randomised trials	none	none	none	serious[2,3]	none	12/67 (17.9%)	11/85 (12.9%)	OR 1.34 (1.42 to 4.28)	37 more per 1000 (from 45 more to 259 more)	MODERATE
Any Grade 3/4/ LENT-SOM toxicity at anytime during follow-up											
1[1]	randomised trials	none	none	none	serious[2,3]	none	35/61 (57.4%)	38/78 (48.7%)	OR 1.65 (0.67 to 4.06)	123 more per 1000 (from 98 fewer to 307 more)	MODERATE
Metastases-free survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Huddart et al. 2013 (BC20001 trial) [2] Low number of events limits precision [3] Wide confidence intervals limits precision

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Table 90: GRADE evidence profile: What is the optiam radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer? Comparison: Accelerated fractionation versus conventional fractionation radiotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AF	CF	Relative (95% CI)	Absolute	Quality
Relapse-free survival											
1[1]	randomised trials	none	none	none	serious[2,3]	none	68/129 (52.7%)	49/100 (49%)	HR 1.00 (0.69 to 1.45)	5-yr RFS 39% AF vs 32% CF, uncertainty of difference	MODERATE
Overall survival (mortality rate)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	74/129 (57.4%)	56/100 (56%)	RR 1.02 (0.81 to 1.29)	5-yr OS 37% AF vs 40% CF, uncertainty of difference	MODERATE
Local failure											
1[1]	randomised trials	none	none	none	serious[2,3]	none	41/129 (31.8%)	29/100 (29%)	RR 1.17 (0.79 to 1.73)	2-yr local control 68% AF vs 65% CF, uncertainty of difference	MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	none	serious[2,3]	none	2/129 (1.6%)	0/100 (0%)	RR 3.88 (0.19 to 80.02)	-	MODERATE
Late radiation toxicity											
1[1]	randomised trials	none	none	none	serious[2,3]	none	57/129 (44.2%)	35/100 (35%)	RR 1.26 (0.91 to 1.76)	91 more per 1000 (from 31 fewer to 266 more)	MODERATE
Acute bowel toxicity (assessed with: Grade 2-3 RTOG)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	53/121 (43.8%)	25/96 (26%)	RR 1.68 (1.14 to 2.49)	177 more per 1000 (from 36 more to 388 more)	MODERATE
Acute bladder toxicity (assessed with: Grade 2-3 RTOG)											
1[1]	randomised trials	none	none	none	serious[2,3]	none	42/121 (34.7%)	34/96 (35.4%)	RR 0.98 (0.68 to 1.41)	7 fewer per 1000 (from 113 fewer to 145 more)	MODERATE
Health-related quality of life											
0	No evidence available										

[1] Horwich et al. 2005 [2] Low number of events limits precision [3] Confidence interval includes null value

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Table 91: GRADE evidence profile: What is the optiam radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer? Comparison: Neoadjuvant MVC and RT versus Concurrent cisplatin CRT

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant CT+RT, n=41	Concurrent CRT, n=39	Relative (95% CI)	Absolute	
Overall survival (follow-up median 72 months)											
1[1]	observational studies	none	none	none	serious[2]	none	5-yr OS 73% not reported separately		-	No difference between protocols (p=.820)	VERY LOW
Cancer-specific survival (follow-up median 72 months)											
1[1]	observational studies	none	none	none	serious[2]	none	5-yr CSS 82% not reported separately		-	No difference between protocols (p=.688)	VERY LOW
Distant metastases (follow-up median 72 months)											
1[1]	observational studies	none	none	none	serious[2]	none	Rate not reported		-	No difference between protocols (p value not reported)	VERY LOW
Disease-free survival (follow-up median 72 months)											
1[1]	observational studies	none	none	none	serious[2]	none	67%	82%	-	Favours CRT (p=.031)	VERY LOW
Urinary toxicity, Grade 2 or higher (assessed with: RTOG)											
1[1]	observational studies	none	none	none	serious[2]	none	5/41 (12.2%)	13/39 (33.3%)	RR 0.37 (0.14 to 0.93)	210 fewer per 1000 (from 23 fewer to 287 fewer)	VERY LOW
GI toxicity Grade 2 or higher (assessed with: RTOG)											
1[1]	observational studies	none	none	none	serious[2]	none	5/80 (6%) Rate not reported separately		-	No difference between protocols	VERY LOW
Health-related quality of life											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										

[1] *Zapatero et al. 2012* [2] *Low number of events limits precision*

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Table 92: GRADE evidence profile: What is the optiam radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer? Comparison: Neoadjuvant MVC + RT versus Neoadjuvant MVC + Concurrent platinum-based CRT

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT n=43	CRT n=78	Relative (95% CI)	Absolute	Quality
5-year Overall survival (follow-up median 66 months)											
1[1]	observational studies	none	none	none	serious[2]	none	60.4%	71.8%	-	Favours CRT (p=.008)	VERY LOW
5-year Disease-specific survival (follow-up median 66 months)											
1[1]	observational studies	none	none	none	serious[2]	none	62.8%	79.4%	-	Favours CRT (p=.003)	VERY LOW
Acute toxicity: bone marrow (assessed with: WHO criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	6/43 (14%)	13/78 (16.7%)	RR 0.84 (0.34 to 2.04)	27 fewer per 1000 (from 110 fewer to 173 more)	VERY LOW
Acute toxicity: bladder (assessed with: WHO criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	6/43 (14%)	9/78 (11.5%)	RR 1.21 (0.46 to 3.17)	24 more per 1000 (from 62 fewer to 250 more)	VERY LOW
Acute toxicity: intestinal (assessed with: WHO criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	4/43 (9.3%)	11/78 (14.1%)	RR 0.66 (0.22 to 1.95)	48 fewer per 1000 (from 110 fewer to 134 more)	VERY LOW
Health-related quality of life											
0	No evidence available										
Metastases-free survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										

[1] *Perdona et al. 2008* [2] *Low number of events limits precision*

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Table 93: GRADE evidence profile: What is the optiam radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer? Comparison: RT only versus Concurrent CRT

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RT, n=142**	**CRT, n=331**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival (follow-up median 71.5 months)											
1[1]	observational studies	serious[2]	none	none	serious[3]	none	Median 28.5 months	Median 70 months	-	Favours CRT (p<0.001)	VERY LOW
Disease-free survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Metastases-free survival											
0	No evidence available										
Urinary function (lacking control in previous 7 days)											
1[4]	observational studies	none	none	none	serious[5]	none	n/a	9/48 (19%)	-	-	VERY LOW
Bowel function (difficulty in control in previous 7 days)											
1[4]	observational studies	none	none	none	serious[5]	none	n/a	10/48 (22%)	-	-	VERY LOW
Quality of life (measured with: SF-36; Physical functioning overall mean; range of scores: 0-100; Better indicated by higher values)											
1[4]	observational studies	none	none	none	serious[5]	none	n/a	Mean=89	-	-	VERY LOW
Quality of life (measured with: SF-36; General health perceptions; range of scores: 0-100; Better indicated by higher values)											
1[4]	observational studies	none	none	none	serious[5]	none	n/a	Mean=74	-	-	VERY LOW

[1] Krause et al. 2011 [2] Patient characteristics not reported separately for treatment protocols. Unclear if groups were comparable at baseline. [3] Low number of events limits precision [4] Zietman et al. 2003 [5] Small sample size limits precision

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Table 94: GRADE evidence profile: What is the optiam radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer? Comparison: Conventional single-phase RT to whole bladder versus two-phase reduced volume treatment

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Two-phase RT, n=75	Conventional RT, n=154	Relative (95% CI)	Absolute	Quality
Overall survival (follow-up median 4.8 years)											
1[1]	observational studies	none	none	none	serious[2,3]	none	Median 2.8y	Median 2.8y	HR 0.91 (0.64 to 1.3)	-	VERY LOW
Disease-free survival											
0	No evidence available										
Metastases-free survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Grade 3 incontinence risk at 5-yr (assessed with: RTOG criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	19%	30%	HR 0.41 (0.2 to 0.81)	Favours two-phase RT	VERY LOW
Overall Grade 3-4 late effects (assessed with: RTOG criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	13/53 (24.5%)	42/96 (43.8%)	RR 0.56 (0.33 to 0.95)	Favours two-phase RT, 19% reduction in late effects	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Mangar et al. 2006 [2] Small sample size limit precision [3] Confidence interval includes null value

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Table 95: GRADE evidence profile: What is the optiam radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer? Comparison: Concomitant CRT with Gemcitabine versus RT alone

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT	RT	Relative (95% CI)	Absolute	Quality
Overall survival (follow-up median 18 months)											
1[1]	observational studies	none	none	none	serious[2]	none	N =23 3-yr 38%	N=46 3-yr 27%	Not reported	-	VERY LOW
Disease-free survival											
0	No evidence available										
Metastases-free survival											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Increased urine frequency during treatment (assessed with: FACT-BL)											
1[3]	observational studies	none	none	none	serious[2]	none	11/13 (85%)	n/a	-	-	VERY LOW
Health-related quality of life (measured with: FACT-BL and FACT-G; Better indicated by lower values)											
1[3]	observational studies	none	none	none	serious[2]	none	N=23	n/a	-	No significant change before, during or after treatment	VERY LOW

[1] Asadauskiene et al. 2010 [2] Small sample size limits precision [3] Herman et al. 2004

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Use a radiosensitiser (such as mitomycin in combination with fluorouracil [5-FU][f] or carbogen in combination with nicotinamide[g]) when giving radical radiotherapy (for example, 64 Gy in 32 fractions over 6.5 weeks or 55 Gy in 20 fractions over 4 weeks) for muscle-invasive urothelial bladder cancer.**
Relative value placed on the outcomes considered	The GDG considered all of the outcomes specified in the PICO as important for people receiving treatment for muscle-invasive bladder cancer. These included • Overall survival • Disease-free survival • Treatment-related morbidity • Treatment-related mortality • Health-related quality of life, inc patient reported outcomes • Metastases free survival Loco-regional recurrence free survival was not specified in the PICO but was used to make recommendations because this was a primary outcome in the BC2001 randomised trial and was considered the most relevant end-point. This outcome was supported by improvements in metastases-free survival in the trial.
Quality of the evidence	The evidence was assessed with GRADE as being of very low to moderate quality. The GDG considered the limitations of the evidence. Notably, the wide confidence intervals in the accelerated radiotherapy study meant the GDG could not infer non-inferiority of the regimen and therefore the GDG did not recommend accelerated fractionation radiotherapy The age of the included studies limits the applicability of the evidence to current UK practice. Both randomised trials were devised in the late 1990s and newer systemic agents are currently in use. Aside from the randomised trials, much of the data regarding other chemosensitisers came from retrospective observational studies and small phase 2 studies, which diluted the strength of the recommendation about precisely which agents the GDG could recommend. The GDG felt that the evidence of benefit for a radiosensitisation (either chemotherapy or Carbogen/Nicotinamide) was clearly demonstrated by

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

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

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	the evidence and the limitations were not pertinent to these views. There was evidence to support both treatment approaches, but it was unclear as to which was superior and therefore both have been recommended as treatment options. The GDG considered that although there is evidence which suggests that radiotherapy with a chemosensitiser is more beneficial than radiotherapy alone, there is uncertainty as to which patients will benefit from the use of chemotherapy and which will benefit most from the use of Carbogen plus Nicotinamide and/or whether they will benefit more from using both drugs. The research recommendation will help to clarify which patients are most likely to benefit from the use of a chemosensitiser.
Trade-off between clinical benefits and harms	The GDG considered that the main benefit from these recommendations is improved treatment outcomes for patients and this was weighed against the possible increased toxicity to patients. The GDG considered that there was more evidence for better outcomes without excessive increased toxicity. The benefit of improved survival and local control was considered to outweigh harms.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG considered that there are potential savings due to improved outcomes for patients e.g. fewer cystectomies, reduced treatment for metastases and reduced palliative care costs. The potential costs from the recommendations include the costs of increased use of radiosensitisers and more preserved bladders with the associated increase in cystoscopic follow-up. The GDG feels the recommendations are likely to be cost-effective in cost per QALY terms.
Other considerations	No equality issues were identified. The GDG considered the potential change in practice required to implement the recommendation. They noted that a significant number of UK centres are currently using radiosensitisation but there are likely to be a number of centres which have not, to date, adopted this treatment. There is also a potential need for more surveillance resulting from the recommendations.

Research recommendation	**Can biomarkers accurately predict the effectiveness of radiosensitisers (for example mitomycin C and 5-FU or carbogen and nicotinamide) in muscle-invasive bladder cancer treated with radical radiotherapy?**
Why is this important	There is some evidence that response to the use of radiosensitisers with radical radiotherapy varies with biomarker expression. Reliable prediction of which radiosensitiser (carbogen or Mitomycin/5-FU) to use when treating a person with muscle invasive bladder cancer with radiotherapy, would improve cancer treatment outcomes and reduce the need for consideration of salvage cystectomy. It would be a step towards personalised medicine. The question is of high importance and applicable to thousands of people with bladder cancer across England and Wales. It would probably result in no overall increase in the use of radiotherapy, and would have cost consequences in laboratory staff capacity and consumables. There would probably be savings through more

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	appropriate use of both radiotherapy and less need for salvage cystectomy. There would be no equality consequence, and the logistics of the research would be deliverable.

5.2.3 Urinary stoma versus bladder reconstruction.

After radical cystectomy, drainage of urine has to be re-established. This can be done by using bowel either to create a urinary stoma or some form or urinary reconstruction. A urinary stoma necessitates continuous drainage into an external bag. Urinary reconstruction involves either a bladder substitute, or a catheterisable reservoir

Rehabilitation after radical cystectomy is much quicker with a stoma than with urinary reconstruction. The majority of people with a stoma learn very quickly how to empty and change their bag but will have a piece of bowel at the skin surface and will need an external bag for the rest of their life. Bladder reconstruction leaves only a scar, and no external bag. A bladder substitute allows urine to be held and passed in a more or less normal way, and a catheterisable reservoir is emptied by passage of a catheter around three to four times each day. Learning how to use and care for a bladder substitute or a catheterisable reservoir requires much more time and diligence in the short and longer term than learning how to use a stoma.

There is variation in both provision of bladder reconstruction and which options are presented to patients resulting in large variations in accessibility which are neither related to outcomes or choice.

Clinical question: Is bladder reconstruction or urinary stoma the more effective method of urinary diversion?

Clinical evidence (see also full evidence review)

The evidence is summarised in tables 96 and 97.

Evidence statements

Low quality evidence from one systematic review of 557 studies (46,921 patients) (Somani et al., 2009) assessing adverse events associated with type of urinary diversion indicates uncertainty over the most effective surgical option. Whilst the percentage of patients reporting some adverse events varied depending on type of urinary diversion (in some instances varied considerably according to study design) none of the differences presented reached statistical significance (unclear how this was assessed as no statistical analyses are presented in the article). Somani et al. (2009) proposed that the lack of statistical significance does not provide evidence of lack of equivalence or evidence of lack of superiority of one intervention over the other but could be attributable to better patient selection for type of urinary diversion (e.g. younger and fitter patients undergoing bladder replacement).

Prospective studies favoured ileal conduit for fewer operative complications compared to the continent diversions (6.1% versus 25.7%, respectively). However, postoperative morbidity favoured the continent diversions compared to ileal conduit (11.4% versus 27%, respectively).

More upper tract UTIs were reported in the ileal conduit patients compared to the continent diversions patients (26.5% versus 8.1%, respectively). Further, Ileal conduit patients reported more metabolic alkalosis (23.8% versus 2.7%), higher rates of bone disease (70.4% of ileal conduit patients versus 19.8% of continent patients), and increased problems with odour (67.6% versus 28.6%) compared to continent diversion patients.

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A higher incidence of urinary stones were reported in the continent diversion patients (14.1% [prospective studies] and 15.9% [retrospective studies]) compared to the ileal conduit patients versus (5.2% [retrospective studies]). In addition, continent diversion patients reported higher rates of faecal incontinence (10.8% of continent patients versus 0% of ileal conduit patients) and flatus leakage (28.6% of continent patients versus 5% of ileal conduit patients) compared to the ileal conduit patients.

There was no comparative data for lower tract UTIs or clean intermittent self-catheterisation but in both adverse events over 20% of continent patients reported these issues (prospective data: 23.8% lower tract UTIs; 28.3% clean intermittent self-catheterisation). No comparative for prospective studies was found comparing types of diversion for metabolic acidosis, with 39.4% of continent diversion patients reporting this event. However, comparative data for retrospective studies reported a higher frequency of the adverse event in the continent patients compared to ileal conduit patients (25.0% versus 3.1%, respectively).

Health related quality of life and patient satisfaction was reported by one low quality systematic review of 46 studies (4,186 patients) (Somani et al., 2010) and ten very low quality observational studies (725 patients) (Erber et al., 2012; Gacci et al., 2013; Harano et al., 2007; Metcalfe et al., 2013; Sherwani et al., 2009; Vakalopoulos et al., 2011; Shim et al., 2014; Asgari et al., 2013a; Asgari et al., 2013b; Singh et al., 2014) . The majority of the 56 studies reviewed reported that patients had good HRQoL/global satisfaction (13/56 studies: 23%) or that there were no statistically significant differences between the groups compared on HRQoL/satisfaction (19/56 studies: 34%). Of the remaining studies 20/56 (36%) reported that there were differences between the groups compared. The systematic review provided minimal information on these statistically differences, and implied that the pooled results reveal inconsistent findings across the different types of urinary diversions. For example, three studies reported poorer outcomes for patients receiving an orthotopic bladder replacement compared to patients receiving ileal conduit diversions or control participants (e.g. more urinary leakage; reduced physical health, reduced emotional problems and higher bodily pain; low body image), whereas three other studies reported better outcomes for these orthotopic bladder patients (e.g. HRQoL better in all domains; higher physical functioning). Inconsistent results across the different types of urinary diversions were also found in the ten very low quality observational studies. In addition, the majority of these significant differences were in one or two sub-scale analyses and did not reflect global HRQoL differences between the compared groups.

Four studies (two retrospective, two prospective) out of the 46 studies included in the low quality systematic review (Somani et al., 2010) assessed the impact of psychological interventions (e.g. pre-operative counselling [no additional information provided on what the “interventions” were, how they were measured]) on HRQoL and patient satisfaction outcomes. The two retrospective studies reported an increase in satisfaction scores post-surgery following pre-operative counselling.

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Table 96: GRADE evidence profile: Is bladder reconstruction or urinary stoma the more effective method of urinary diversion? Urinary diversions and adverse events

Note: The Continent diversions category was computed by summing any data reported for each adverse event from the following groups of patients in the Somani (2009) review article: continent diversion patients (continent cutaneous diversion, ureterosigmoidostomy and the newer variants of ureterosigmoidostomy), bladder reconstruction patients (native bladder remains in situ and is surgically manipulated to improve its function) and bladder replacement patients (native bladder was removed completely and a new reservoir was created, positioned where the native bladder used to be and connected to the native urethra, therefore, allowing patients to void in the natural way).

Quality assessment							Summary of findings				
									Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Relative (95% CI)	Absolute	Quality
Postoperative morbidity - Ileal conduit Prospective											
13[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	317/1175 (27%)	-	-	-	LOW
Postoperative morbidity - Continent diversions Prospective											
13[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	87/766 (11.4%)	-	-	-	LOW
Postoperative morbidity - Ileal conduit Retrospective											
134[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	555/2317 (24%)	-	-	-	LOW
Postoperative morbidity - Continent diversions Retrospective											
134[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	1663/9294 (17.9%)	-	-	-	LOW
Postoperative mortality - Ileal conduit Prospective											
15[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	29/1159 (2.5%)	-	-	-	LOW
Postoperative mortality - Continent diversions Prospective											
15[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	55/2175 (2.5%)	-	-	-	LOW
Postoperative mortality - Ileal conduit Retrospective											
106[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	82/1911 (4.3%)	-	-	-	LOW
Postoperative mortality - Continent diversions Retrospective											
106[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	361/8628 (4.2%)	-	-	-	LOW
Operative complications - Ileal conduit Prospective											
2[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	8/132 (6.1%)	-	-	-	LOW

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Quality assessment							Summary of findings				
									Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Relative (95% CI)	Absolute	Quality
Operative complications - Continent diversions Prospective											
2[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	9/35 (25.7%)	-	-	-	LOW
Operative complications - Ileal conduit Retrospective											
30[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	47/365 (12.9%)	-	-	-	LOW
Operative complications - Continent diversions Retrospective											
30[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	174/1633 (10.7%)	-	-	-	LOW
Need for reoperation - Ileal conduit Prospective											
17[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	3/116 (2.6%)	-	-	-	LOW
Need for reoperation - Continent diversions Prospective											
17[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	141/13611 (1%)	-	-	-	LOW
Need for reoperation - Ileal conduit Retrospective											
190[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	270/1673 (16.1%)	-	-	-	LOW
Need for reoperation - Continent diversions Retrospective											
190[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	1316/10895 (12.1%)	-	-	-	LOW
Bowel anastomotic leakage - Continent diversions Prospective											
1	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	1/33 (3%)	-	-	-	LOW
Bowel anastomotic leakage - Ileal conduit Retrospective											
39[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	19/724 (2.6%)	-	-	-	LOW
Bowel anastomotic leakage - Continent diversions Retrospective											
39[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	95/3069 (3.1%)	-	-	-	LOW
Bladder/ureteroenteric anastomtic leakage - Continent diversions Prospective											
3	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	15/309 (4.9%)	-	-	-	LOW
Bladder/ureteroenteric anastomtic leakage - Ileal conduit Retrospective											
45[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	37/999 (3.7%)	-	-	-	LOW
Bladder/ureteroenteric anastomtic leakage - Continent diversions Retrospective											
45[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	202/3719 (5.4%)	-	-	-	LOW
Upper tract Urinary Tract Infection - Ileal conduit Prospective											

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Quality assessment							Summary of findings				
									Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Relative (95% CI)	Absolute	Quality
14[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	13/49 (26.5%)	-	-	-	LOW
Upper tract Urinary Tract Infection - Continent diversions Prospective											
14[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	55/682 (8.1%)	-	-	-	LOW
Upper tract Urinary Tract Infection - Ileal conduit Retrospective											
101[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	167/3080 (5.4%)	-	-	-	LOW
Upper tract Urinary Tract Infection - Continent diversions Retrospective											
101[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	454/6396 (7.1%)	-	-	-	LOW
Lower tract Urinary Tract Infection - Continent diversions Prospective											
7	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	284/1192 (23.8%)	-	-	-	LOW
Lower tract Urinary Tract Infection - Continent diversions Retrospective											
70	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	368/3070 (12%)	-	-	-	LOW
Clean intermittent self-catheterisation - Continent diversions Prospective											
9	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	230/814 (28.3%)	-	-	-	LOW
Clean intermittent self-catheterisation - Continent diversions Retrospective											
8[3]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	1458/4644 (31.4%)	-	-	-	LOW
Catheter blockage - Continent diversions Prospective											
2	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	9/136 (6.6%)	-	-	-	LOW
Catheter blockage - Continent diversions Retrospective											
1[5]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	64/1566 (4.1%)	-	-	-	LOW
Diarrhea - Ileal conduit Prospective											
3[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	10/76 (13.2%)	-	-	-	LOW
Diarrhea - Continent diversions Prospective											
3[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	17/151 (11.3%)	-	-	-	LOW
Diarrhea - Ileal conduit Retrospective											
36[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	9/210 (4.3%)	-	-	-	LOW
Diarrhea - Continent diversions Retrospective											
36[1]	observational	no serious	no serious	no serious	no serious	none[3,7]	203/2592	-	-	-	

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Quality assessment							Summary of findings				
									Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Relative (95% CI)	Absolute	Quality
	studies[2]	limitations[3,7]	inconsistency[3,7]	indirectness[3,7]	imprecision[3,7]		(7.8%)				LOW
Stress incontinence - Continent diversions Prospective											
1[5]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	29/958 (3%)	-	-	-	LOW
Stress incontinence - Ileal conduit Retrospective											
54[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	1/20 (5%)	-	-	-	LOW
Stress incontinence - Continent diversions Retrospective											
54[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	231/3330 (6.9%)	-	-	-	LOW
Odor - Ileal conduit Prospective											
2[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	23/34 (67.6%)	-	-	-	LOW
Odor - Continent diversions Prospective											
2[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	6/21 (28.6%)	-	-	-	LOW
Odor - Ileal conduit Retrospective											
3[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	34/58 (58.6%)	-	-	-	LOW
Odor - Continent diversions Retrospective											
3[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	7/115 (6.1%)	-	-	-	LOW
Stomal stenosis - Continent diversions {Prospective											
2	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	9/81 (11.1%)	-	-	-	LOW
Stomal stenosis - Ileal conduit Retrospective											
88[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	81/1860 (4.4%)	-	-	-	LOW
Stomal stenosis - Continent diversions Retrospective											
88[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	556/5023 (11.1%)	-	-	-	LOW
Hernia - Ileal conduit Retrospective											
35[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	45/1227 (3.7%)	-	-	-	LOW
Hernia - Continent diversions Retrospective											
35[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	65/2746 (2.4%)	-	-	-	LOW
Faecal urgency - Ileal conduit Retrospective											
5[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	0/29 (0%)	-	-	-	LOW

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Quality assessment							Summary of findings				
									Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Relative (95% CI)	Absolute	Quality
Faecal urgency - Continent diversions Retrospective											
5[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	15/347 (4.3%)	-	-	-	LOW
Faecal incontinence - Ileal conduit Retrospective											
5[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	0/29 (0%)	-	-	-	LOW
Faecal urgency - Continent diversions Retrospective											
5[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	32/295 (10.8%)	-	-	-	LOW
Flatus leakage - Ileal conduit Retrospective											
2[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	5/100 (5%)	-	-	-	LOW
Flatus leakage - Continent diversions Retrospective											
2[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	8/28 (28.6%)	-	-	-	LOW
Constipation - Ileal conduit Retrospective											
7[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	9/122 (7.4%)	-	-	-	LOW
Constipation - Continent diversions Retrospective											
7[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	25/181 (13.8%)	-	-	-	LOW
Upper tract dilation - Continent diversions Prospective											
1[4]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	163/1059 (15.4%)	-	-	-	LOW
Upper tract dilation - Ileal conduit Retrospective											
119[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	192/1482 (13%)	-	-	-	LOW
Upper tract dilation - Continent diversions Retrospective											
119[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	756/4578 (16.5%)	-	-	-	LOW
Uterointestinal stenosis - Ileal conduit Prospective											
19[1]	observational studies[2]	no serious limitations[3,4]	no serious inconsistency[3,4]	no serious indirectness[3,4]	no serious imprecision[3,4]	none[3,4]	14/126 (11.1%)	-	-	-	LOW
Uterointestinal stenosis - Continent diversions Prospective											
19[1]	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	84/1658 (5.1%)	-	-	-	LOW
Uterointestinal stenosis - Ileal conduit Retrospective											
134[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	131/1625 (8.1%)	-	-	-	LOW
Uterointestinal stenosis - Continent diversions Retrospective											

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Quality assessment							Summary of findings				
									Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Relative (95% CI)	Absolute	Quality
134[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	708/6124 (11.6%)	-	-	-	LOW
Renal failure - Continent diversions Prospective											
8	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	32/239 (13.4%)	-	-	-	LOW
Renal failure - Ileal conduit Retrospective											
91[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	76/1744 (4.4%)	-	-	-	LOW
Renal failure - Continent diversions Retrospective											
91[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	297/4006 (7.4%)	-	-	-	LOW
Metabolic acidosis - Continent diversions Prospective											
9	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	404/1025 (39.4%)	-	-	-	LOW
Metabolic acidosis - Ileal conduit Retrospective											
117[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	18/585 (3.1%)	-	-	-	LOW
Metabolic acidosis - Continent diversions Retrospective											
117[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	1008/4029 (25%)	-	-	-	LOW
Metabolic alkalosis - Ileal conduit Retrospective											
16[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	24/101 (23.8%)	-	-	-	LOW
Metabolic alkalosis - Continent diversions Retrospective											
16[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	12/449 (2.7%)	-	-	-	LOW
Urinary stones - Continent diversions Prospective											
10	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	194/1379 (14.1%)	-	-	-	LOW
Urinary stones - Ileal conduit Retrospective											
138[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	90/1720 (5.2%)	-	-	-	LOW
Urinary stones - Continent diversions Retrospective											
138[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	953/6005 (15.9%)	-	-	-	LOW
Vitamin B12 deficiency - Continent diversions Prospective											
2	observational studies[2]	no serious limitations[3,5]	no serious inconsistency[3,5]	no serious indirectness[3,5]	no serious imprecision[3,5]	none[3,5]	2/138 (1.4%)	-	-	-	LOW
Vitamin B12 deficiency - Ileal conduit Retrospective											
29[1]	observational	no serious	no serious	no serious	no serious	none[3,6]	9/157 (5.7%)	-	-	-	

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Quality assessment							Summary of findings				
									Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Relative (95% CI)	Absolute	Quality
	studies[2]	limitations[3,6]	inconsistency[3,6]	indirectness[3,6]	imprecision[3,6]						LOW
Vitamin B12 deficiency - Continent diversions Retrospective											
29[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	76/694 (11%)	-	-	-	LOW
Bone disease - Ileal conduit Retrospective											
8[1]	observational studies[2]	no serious limitations[3,6]	no serious inconsistency[3,6]	no serious indirectness[3,6]	no serious imprecision[3,6]	none[3,6]	19/27 (70.4%)	-	-	-	LOW
Bone disease - Continent diversions Retrospective											
8[1]	observational studies[2]	no serious limitations[3,7]	no serious inconsistency[3,7]	no serious indirectness[3,7]	no serious imprecision[3,7]	none[3,7]	52/263 (19.8%)	-	-	-	LOW

[1] Data from systematic review by Somani et al. (2009). Number of studies is provided according to prospective/retrospective and not broken down by urinary diversion. For each adverse event that is from prospective data the number of studies will not differ between ileal conduit and continent diversions. For each adverse event that is from retrospective data the number of studies will not differ between ileal conduit and continent diversions. [2] Study design unknown for each adverse event as authors categorise studies into prospective and retrospective with no further break down of design. [3] Author's assessed study quality according to a checklist (unclear whether checklist developed by the authors). Score total = 27. Author's only provided average total score according to pooled studies (e.g., retrospective versus prospective) and not according to each adverse event so no information can be assessed on quality of study design per adverse event outcome. [4] For the Ileal conduit prospective studies the study quality mean score (assessed by the author's quality checklist) was 9.75/27. [5] For the Continent diversions prospective studies the study quality mean score (assessed by the author's quality checklist) was 9.22/27. [6] For the Ileal conduit retrospective studies the study quality mean score (assessed by the author's quality checklist) was 7/27. [7] For the Continent diversions retrospective studies the study quality mean score (assessed by the author's quality checklist) was 7.4/27.

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Table 97: GRADE evidence profile: Is bladder reconstruction or urinary stoma the more effective method of urinary diversion? Urinary diversions and Health Related Quality of Life (HRQoL) and Patient Satisfaction

Quality assessment							Summary of findings				
									Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Control	Relative (95% CI)	Absolute	Quality
HRQOL and Patient Satisfaction Systematic Review (Somani et al. 2010)											
46[1]	observational studies	no serious limitations[2]	no serious inconsistency[2]	no serious indirectness[2]	no serious imprecision[2]	none[2]	4186	-	-	-	LOW
HRQOL and Patient Satisfaction											
10	observational studies	no serious limitations	no serious inconsistency	serious[3]	no serious imprecision	none	725	-	-	-	VERY LOW

[1] Data from systematic review by Somani et al. (2010). [2] No assessment of study quality presented in article. Paragraph in discussion summarising quality, mentioning some limitations of all included studies (e.g. selection bias, non-randomised, no baseline measurement). [3] Variation in scales used across included studies (Sherwani et al. 2009 used a self-designed non-validated scales) and in the interpretation of the validated scales used (e.g. sub-scale totals and total scores differed across studies using the same scales). Variation in the methods used to collect the data with two studies (Gacci et al. 2013; Sherwani et al. 2009) being unclear on how data were obtained from the participants (e.g. during consultation, self-assessed). In addition, almost half of the included articles failed to explain how to interpret the numbers provided in the results regarding the QoL scales (e.g. high or low quality of life).

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer people who have chosen radical cystectomy a urinary stoma, or a continent urinary diversion (bladder substitution or a catheterisable reservoir) if there are no strong contraindications to continent urinary diversion such as cognitive impairment, impaired renal function or significant bowel disease.** **Members of the specialist urology multidisciplinary team (including the bladder cancer specialist urological surgeon, stoma care nurse and clinical nurse specialist) should discuss with the person whether to have a urinary stoma or continent urinary diversion, and provide opportunities for the person to talk with people who have had these procedures.**
Relative value placed on the outcomes considered	The GDG considered treatment-related morbidity, adverse events, patient satisfaction, and health-related quality of life as important outcomes because they influence the treatment decisions made by patients. The GDG also considered it important to know that treatment-related mortality was similar between the two options for urinary diversion. All outcomes from the PICO were reported in the evidence and no additional outcomes (i.e. not specified in the PICO) were used to make recommendations.
Quality of the evidence	The evidence was of very low quality as assessed with GRADE. The main limitations of the evidence were that the included studies were mostly retrospective studies, and there were no controlled studies comparing the interventions.It was difficult to compare studies because they used different metrics for assessing quality of life. Because of these limitations the GDG could not conclude that one urinary diversion method was better than the other. The recommendation for discussion between the patient and the multidisciplinary team and other patients was based on clinical consensus because there was minimal and conflicting evidence about the efficacy of pre-operative counselling. The GDG considered their knowledge that large numbers of patients are currently not being offered a choice of urinary diversion. The GDG considered it highly important for people to have the opportunity to discuss options for urinary diversion with trained multi-disciplinary team members and with patients who have undergone these procedures. No research recommendation was made. The GDG were aware of an ongoing quality of life study (OTIS study) in this area.
Trade-off between clinical benefits and harms	The GDG considered the benefits of the recommendations made to be improved informed decision making and increased choice for patients and improved quality of life. The GDG noted that there is a risk that during implementation the

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	recommendation may lead to procedures being carried out by surgeons with inadequate training in bladder reconstruction. However, current commissioning and governance arrangements should mitigate against the risk of harm. The benefits to patients are thought to outweigh the risks.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG considered potential costs and savings of the recommendations. There may be travel costs to patients when their preferred diversion method is not available locally. There may be an increase in reconstructive surgery which is more expensive, increased specialist nurse involvement, extra time for consultation with patients, training costs, expenses for patient and carer discussion with other patients, more catheters and washout equipment for neobladders. The potential savings include reduced stoma care and use of disposables. The GDG considered that the recommendations will incur a net cost increase.
Other considerations	The GDG are aware of contemporary NHS evidence indicating inequality of access to a choice of urinary diversion by cancer network, and suggesting that there may be inequality by gender, age, socioeconomic status and ethnicity. In the recommendations, the GDG suggested that cognitive impairement may be a contraindication to bladder reconstruction. The GDG considered that there will be a need for substantial change in practice due to an increase in the numbers of discussions between patients and health care professionals and a potential increase in reconstructive surgery.

5.3 Managing side effects of treatment for muscle-invasive bladder cancer

The management of side effects of treatment for muscle invasive bladder cancer was investigated alongside the management of side effects of treatment for non-muscle-invasive bladder cancer. Recommendations on this can be found in section 4.4.

5.4 Follow-up after radical treatment of organ confined muscle-invasive bladder cancer

People previously treated for muscle invasive bladder cancer are at high risk of recurrence. These may occur locally and/or as distant metastases. The majority of recurrences are ultimately fatal. The goal of any follow-up protocol is appropriate detection of recurrences such that treatment outcomes may be optimised. Furthermore, people who have had radical cystectomy need additional follow-up related to the anatomical and functional consequences of their surgery.

Follow-up protocols should therefore define the type and frequency of tests necessary to diagnose recurrences. Follow up protocols currently include imaging and urine tests, as well as cystoscopy (for people who have had radical radiotherapy) and urethroscopy (for people who have had radical cystectomy). There is variation in current follow-up protocols many of which are not evidence based. People who have had radical surgery, radical radiotherapy or non-curative treatment may require different follow-up protocols. In addition patients may develop symptomatic recurrences between follow-up visits.

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Nomograms have been developed to predict the risk of recurrence for an individual patient but these have not been widely validated. However, they may be useful in allowing a stratified approach to follow-up based on risk and site of recurrence and thus inform the type and frequency of follow-up tests.

People with bladder cancer are at increased risk of developing upper tract urothelial cancer and there is considerable variation in practice regarding detection of these cancers.

Clinical question: What is the optimal follow-up protocol for muscle invasive bladder cancer?

Clinical evidence (see also full evidence review)

The evidence is summarised in table 98. There was no direct evidence about the optimum follow-up protocol for muscle invasive bladder cancer.

Evidence statements

Follow-up after radical cystectomy

Low quality evidence from eight observational studies including 6,398 patients report overall recurrence rates of between 20% and 46% after radical cystectomy. Most studies report that the risk of both recurrence and metastasis increases with the stage of the primary tumour.

The proportion of asymptomatic recurrences detected by routine follow-up reported in four studies is 12% (Volkmer *et al.*, 2009), 10% (Slaton *et al.*, 1999), 22% (Boorjian *et al.*, 2011) and 34% (Nieuwenhuijzen *et al.*, 2014) indicating that the majority of recurrences are diagnosed through symptom-driven examinations.

One observational study of 574 patients (Perlis *et al.*, 2013) reported a Finnish cohort which received regular urethral washings for cytology compared to a Canadian cohort where routine cytology was often not performed. Urethral recurrences occurred more often in the Finnish than in the Canadian cohort, but this difference was not statistically significant (6% vs 2.6%, p=0.06) and no difference in overall survival was reported between patients with urethral recurrence at both sites (very low quality evidence).

One study of 479 patients (Giannarini *et al.*, 2010) using a risk-based follow-up protocol (with bone scan and CT scan only if ≥pT3 or T1-4 N+) reports five-year overall survival of 61.9% (95% CI 57.4-66.7%) and five-year disease-specific survival of 69.8% (95% CI 65.5-74.3%). One study of 1599 patients reports that five- and ten-year overall survival is lower in patients with symptomatic recurrence (22% and 10%) than the five- and ten-year overall survival in patients with asymptomatic recurrence (46% and 26%). Patients who were symptomatic at recurrence were at almost 60% increased risk of death than those who were asymptomatic (HR 1.59 (95% CI 1.26 to 2.02) (Boorjian *et al.*, 2011). Similarly, one study of 343 patients reported that patients who were symptomatic at recurrence had shorter survival than those who were asymptomatic (HR 1.58 (p=0.013) (Nieuwenhuijzen *et al.*, 2014).

Very low quality evidence from one observational study of CT urograms reported that findings related to surgery (eg.hydronephrosis, parastomal hernia, urinary tract calculi) were found in 60/105 (57%) of patients during surveillance after radical cystectomy (Shinagare *et al.*, 2013).

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Table 98: GRADE evidence profile: What is the optimal follow-up protocl for muscle-invasive bladder cancer? Follow-up after radical cystectomy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Follow-up	Control	Relative (95% CI)	Absolute	Quality
Local recurrence rate											
8[1]	observational studies	none	none	None	none	none	972/6796 (14.3%)	NA	-	-	LOW
Overall recurrence											
8[2]	observational studies	none	none	None	none	none	2406/6398 (37.6%)	NA	-	-	LOW
Overall survival at 5 years post cystectomy											
1[3]	observational studies	none	none	None	none	none	479	-	-	At 5 years 61.9% (57.4 to 66.7%)	LOW
Disease-specific survival at 5 years post cystectomy											
1[3]	observational studies	none	none	None	none	none	479	-	-	At 5 years 69.8% (65.5 to 74.3%)	LOW
Urethral recurrence (median follow-up 45 months)											
1[4]	observational studies	none	none	None	serious[5]	none	9/151 (6%)	9/352 (2.6%)	RR 2.53 (0.94-5.76)		VERY LOW
Upper urinary tract recurrence (median follow-up 45 months)											
1[4]	observational studies	none	none	None	serious[5]	none	8/205 (3.5%)	13/369 (3.5%)	RR 1.11 (0.47-2.63)		VERY LOW
Overall survival at 10 years											
1[4]	observational studies	none	none	None	serious[6]	none	205	369		No differences between cohorts (p=0.65)	VERY LOW
Distant metastases-free survival											
0	No evidence available										
Treatment-related complications (findings on CTU relating to surgery eg. hydronephrosis, parastomal hernia, urinary tract calculi)											
1[7]	observational studies	none	none	None	serious[5]	none	60/105 (65.7%)	NA	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										
Patient experience/preference											
0	No evidence available										

[1] Yafi et al. 2012, Slaton et al. 1999, Giannarini et al. 2010, Kuroda et al. 2002, Volkmer et al. 2009, Boorjian et al. 2011; Perlis et al. 2013; Nieuwenhuijzen et al. 2014; [2] Yafi et al. 2012, Slaton et al. 1999, Giannarini et al. 2010, Kuroda et al. 2002, Volkmer et al. 2009, Boorjian et al. 2011; Shinagare et al. 2013; Nieuwenhuijzen et al. 2014; [3] Giannarini et al. 2010; [4] Perlis et al. 2013 (routine urethral washings for cytology versus no routine urethral washings); [5] Low number of events/wide confidence intervals limits precision; [6] Number of events not reported; [7] Shinagare et al. 2013

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer follow-up after radical cystectomy or radical radiotherapy.** **After radical cystectomy consider using a follow-up protocol that consists of:** • **monitoring of the upper tracts for hydronephrosis, stones and cancer using imaging and glomerular filtration rate (GFR) estimation at least annually and** • **monitoring for local and distant recurrence using CT of the abdomen, pelvis and chest, carried out together with other planned CT imaging if possible, 6, 12 and 24 months after radical cystectomy and** • **monitoring for metabolic acidosis and B12 and folate deficiency at least annually and** • **for men with a defunctioned urethra, urethral washing for cytology and/or urethroscopy annually for 5 years to detect urethral recurrence.** **After radical radiotherapy consider using a follow-up protocol that includes all of the following:** • **rigid cystoscopy 3 months after radiotherapy has been completed, followed by either rigid or flexible cystoscopy:** - **every 3 months for the first 2 years then** - **every 6 months for the next 2 years then** - **every year thereafter, according to clinical judgement and the person's preference** • **upper-tract imaging every year for 5 years** • **monitoring for local and distant recurrence using CT of the abdomen, pelvis and chest, carried out with other planned CT imaging if possible, 6, 12 and 24 months after radical radiotherapy has finished.**
Relative value placed on the outcomes considered	The GDG considered local recurrence to be particularly important because these recurrences are potentially curable once detected. Other cancer outcomes from the PICO such as overall survival, distant-metastases free survival, disease-specific survival, health-related quality of life, patient experience and patient preference were also considered. These outcomes are important for patients. Treatment-related complication was also considered an important outcome because clinicians are able to intervene more effectively when these complications are detected early. Distant-metastases free survival, health-related quality of life, patient experience and patient preference were not reported in the evidence. No additional outcomes that were not specified in the PICO were used to make recommendations. Survival was not considered to be a useful outcome because of confounding factors in the evidence presented. Differences in survival

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	between patients who are asymptomatic and symptomatic at presentation could reflect lead time bias because they receive the same follow-up and the GDG considered that there is no evidence that early detection of distant recurrence makes any difference to survival.
Quality of the evidence	The overall quality of the evidence for each outcome was low to very low as assessed with GRADE. Some issues with the evidence were presented. Most notably that the evidence was limited to cystectomy series and there was no evidence for follow-up after treatment with radiotherapy. There was also a lack of randomised trial data comparing different follow-up protocols. There were issues of applicability to the current UK population because none of the studies presented were UK studies and included patients who were treated up to 30 years ago. The GDG noted that imaging quality has improved markedly in the past 15 years. Also many issues relating to follow-up were not captured in the evidence. There were also issues with lead-time bias in the survival data as noted above. These issues influenced the GDGs recommendations because the GDG had to use consensus based on clinical experience and knowledge of other evidence not directly captured in the evidence. Patient views were considered regarding the reassurance of regular follow-up care and were balanced against data in other cancers. For example, the GDG considered that there is no evidence from other cancer studies that routine follow-up improves outcomes (for example, data from ovarian cancer suggests routine follow-up does not have a beneficial effect on quality of life). Due to the lack of high quality evidence comparing different follow-up protocols and the issues with the evidence presented, the recommendations were mainly based on clinical experience. Particularly the recommendations about follow-up for patients after treatment with radiotherapy, the metabolic monitoring of patients, the frequency of imaging the kidneys, the type of imaging used, and cytology of the upper tract, as these areas were lacking in evidence. The GDG considered follow up in three situations: after radiotherapy; after surgery; and distant metastatic disease regardless of the modality of treatment. The GDG made a research recommendation due to the uncertainty in the evidence about whether early detection of recurrence improves patient outcomes. The GDG considered it important to address the limited data about varying the intensity of follow-up and its impact on clinical outcomes, NHS resource use and patient-reported outcomes. Despite the weak evidence base, the GDG considered that it was important to make consensus recommendations (as well as a research recommendation) in order to reduce variation of follow-up in current clinical practice. However, the GDG also acknowledged that because of the absence of evidence, it is possible that less intensive follow-up than what has been recommended is necessary. No health economic evidence was identified.
Trade-off between clinical benefits and harms	The GDG considered that a major potential benefit of the recommendations made is the early diagnosis of recurrence which, if treated early, might improve patient survival. Monitoring patients regularly may lead to earlier detection and more effective management of post-operative complications. The GDG noted that there is likely to

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	considerable variation in current practice. The recommendations made should benefit patients by reducing the risks related to over-intensive monitoring. For example, the radiation associated with imaging and morbidity associated with cystoscopy. The GDG considered that the recommendations may increase the likelihood of clinically significant, incidental findings, which are treatable. Thus improving outcomes for patients. A further benefit of follow-up is increased reassurance for patients. The GDG considered the potential harms of the recommendations as less intensive monitoring for some centres and therefore the failure to detect new recurrences. There may also be an increased risk of clinically insignificant incidental findings or significant findings that are not treatable. There may also be increased anxiety for patients undergoing tests and waiting for their results. The GDG reached consensus as to the most appropriate format and intensity of follow-up to maximise potential benefits compared to potential harm. The potential survival benefit, effective management of complications and improvements in patient quality of life were considered to be the key benefits of the recommendations made.
Trade-off between net health benefits and resource use	A health economic model was not developed for this topic and no health economic data was identified. However, the GDG considered the potential costs and savings of the recommendations made. The GDG were unsure of current practice, and suspected there is wide variation. Therefore, the recommendations may reflect a more or less intensive follow-up schedule than current practice. The GDG considered that the key cost trade-off is the potential increased cost of monitoring and imaging weighed against a potential decrease in costs from detecting and treating a cancer early.
Other considerations	The GDG considered that implementing the recommendations is unlikely to involve any equalities issues. The potential change in clinical practice is unknown. The GDG considered that at present many centres will be doing more follow-up and many will be doing less follow-up than the recommendations. It will probably require a lot of change in practice to reduce this variation. When making the recommendations, the GDG also considered the patient/carer representatives views on the value of the reassurance provided from regular follow-up. For the recommendations about follow-up after radiotherapy, the GDG felt cystoscopy should be offered as it is part of the treatment plan and this was mandated in the key trials showing the value of radiotherapy. The GDG decided, based on risk to the patient of recurrence, that the follow-up regimen should be the same as for high-risk non-muscle-invasive bladder cancer. The GDG recognised that some people who receive radiotherapy have impaired performance status and that life-long surveillance is not always appropriate.

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Research recommendation	Is symptom-based review as effective as scheduled follow-up for people treated with radical cystectomy or radical radiotherapy for organ-confined muscle-invasive bladder cancer? Outcomes of interest are overall survival, health-related quality of life, resource use and cost?
Why is this important	Standard care after treatment for organ-confined, muscle-invasive bladder cancer is scheduled follow-up at intervals set out by the treating team. Although this can be reassuring for both the patient and the treating team it is not known whether scheduled follow-up offers clinical benefit compared with symptom-based review which is increasingly used for people with other cancers. Moreover, there are significant costs associated with follow-up. The current evidence about follow-up is confined to cystectomy. There is no evidence concerning follow-up after radiotherapy. In addition, the evidence on radiological follow-up uses mainly outdated imaging techniques.

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6 Managing locally advanced or metastatic bladder cancer

Palliative care services have tended to be requested because of profound physical symptoms in people with terminal bladder cancer. Increasing use of cross sectional imaging is detecting incurable disease much earlier, when there are often no physical symptoms. However the psychological and spiritual impact of a terminal diagnosis will always be profound and input from specialist palliative care at this earlier stage may be of significant benefit. The specialist palliative care needs of people with advanced bladder cancer are covered in section 2.3. This chapter deals with the use of chemotherapy for people with distant metastases and with specific symptoms from locally advanced or metastatic bladder cancer.

6.1 Managing people with distant metastases

Most patients who die of bladder cancer will do so with metastatic disease. The main treatment used to prolong life and palliate/alleviate the symptoms is chemotherapy. Most studies on chemotherapy report benefits in terms of response, symptom control and survival but this comes at the cost of significant treatment related toxicity. Not all patients are able to receive chemotherapy, eg, because of debility, impaired kidney function or over the age for safe use of chemotherapy, and others choose not to have it. There are anecdotal reports of long term survivors, but these are rare. The role of chemotherapy in people who progress or relapse on first line treatment is less clear because their prognosis is usually measured in months, so benefits and drawbacks of chemotherapy are very finely balanced.

Pelvic radiotherapy can also be used to treat patients with symptoms of incurable bladder cancer, especially bleeding from the bladder or pain from the bladder or sites of metastatic spread.

Other forms of specialist intervention may be considered for serious complications of advanced bladder (such as pain, bleeding or upper urinary tract obstruction) including:

- embolisation
- nephrostomy or stent drainage
- nerve blocks

6.1.1 First-line chemotherapy

Chemotherapy is widely used as the first treatment for many people with advanced bladder cancer. Cisplatin based multiagent chemotherapy is most commonly used in people with normal renal function and good performance status.

Many of these people are elderly and/or have impaired performance status and/or impaired renal function. All chemotherapy regimens are associated with a toxicity profile for example sickness, fatigue, neuropathy or myelosuppression.

There is uncertainty about a number of issues related to first line chemotherapy, including:

- Does chemotherapy improve outcomes compared to best supportive care ?
- What is the best regimen?
- Are there subgroups of people who benefit most or least from chemotherapy ?
- What is the best treatment for people who cannot tolerate Cisplatin regimens?

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Clinical question: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

Clinical evidence (see also full evidence review)

The evidence is summarised in tables 99 to 112.

Evidence Statements

Cisplatin-based chemotherapy

One phase II trial (Hillcoat et al., 1989) of 108 participants provided low quality evidence that there was no difference in overall survival between those treated with single agent Cisplatin (C) therapy or a combination of Cisplatin and Methotrexate (CM). Time to progression was longer with CM, but this difference was only significant during the first 12 months of therapy. Toxicity was greater in the CM arm, including haematological toxicity (26% vs. 7%) and mucositis (19% vs. 0%). Single agent Cisplatin was also compared to MVAC in one trial of 246 participants (Loehrer et al., 1992). Overall survival and progression-free survival were greater for MVAC than Cisplatin alone (low quality evidence). At 6-year follow-up, MVAC still showed a survival advantage over Cisplatin (Saxman et al., 1997). However, combined MVAC was more toxic than Cisplatin, with increased rates of grade 3-4 leukopenia, granulocytopenic fever, and mucositis. There were no differences in treatment-related mortality (4% vs. 0%). There was no evidence about health-related quality of life.

One trial (220 participants) of moderate quality reported increased duration of overall survival (14.2 months vs. 9.3 months) and time-to-progression (9.4 months vs. 6.1 months) with MVAC and granulocyte colony-stimulating factor (GCSF) compared to Docetaxel and Cisplatin with GCSF (Bamias et al., 2004). There were no differences in rates of grade 3-4 thrombocytopenia or anaemia. Neutropenia (36% vs. 19%) and neutropenic sepsis were more common in the MVAC arm. There were no differences in treatment-related mortality. One moderate quality trial (263 participants) compared high-dose intensity MVAC and GCSF (HD-MVAC) with classic MVAC (Sternberg et al., 2001a/2006). After a median of 7.3 years follow-up, HD-MVAC produced a small improvement in risk of death and risk of progression. There were lower rates of whole blood cell toxicity and neutropenic fever with HD-MVAC, with no differences between arms for thrombocytopenia, mucositis and treatment-related mortality. Health-related quality of life was not reported.

One phase III trial (405 participants) of MVAC versus Gemcitabine and Cisplatin (GC) providing high quality evidence reported no differences in overall survival and progression-free survival between trial arms (von der Maase et al., 2000/2005). Rates of grade 3-4 anaemia and thrombocytopenia were greater in the GC arm, whereas neutropenia and neutropenic sepsis were more common in the MVAC arm. Mean quality of life scores were not reported but the authors state that quality of life (as measured by the EORTC QLQ C30) was maintained on both arms throughout the study with improvements in emotional functioning and pain. One observational study, where oncology professionals were interviewed as patient representatives, provided very low quality evidence that respondents were more likely to choose GC over MVAC for a reduced incidence of neutropenic sepsis, mucositis, or serious weight loss. Respondents were more willing to accept GC over MVAC even when a hypothetical life expectancy was reduced from 60 weeks to 45 weeks.

One randomised phase III trial (130 patients) of dose dense MVAC versus dose dense GC provided low quality evidence of no difference in overall survival or progression-free survival between groups. Grade 3-5 toxicities were reported in 50% of the DD-MVAC group and 44% of the DD-GC group. Two toxicity-related deaths were both in the DD-MVAC arm due to non-neutropenic sepsis (Bamias et al., 2013).

GC was compared with Pacitaxel, Gemcitabine and Cisplatin (PCG) in one randomised phase II trial of 85 patients (Lorusso et al., 2005) and one randomised phase III trial of 626

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participants (Bellmunt et al., 2012). The phase III trial provided high quality evidence of no difference in overall survival and progression-free survival between trial arms. However, there was a small effect in the subgroup of patients with primary bladder tumours, with longer overall survival in patients treated with PCG (15.9 vs. 11.9 months, HR 0.80, 95% CI 0.66 to 0.97). Grade 3-4 thrombocytopenia was more common in the GC arm, and grade 3-4 neutropenia was more common in the PCG arm (64% vs. 51%). Health-related quality of life was not reported.

Cisplatin-based versus carboplatin-based chemotherapy

Bellmunt et al. (1997) provided low quality evidence, comparing MVAC with methotrexate, carboplatin and vinblastine (M-CAVI) in 47 patients. Median disease-related survival was greater in the MVAC arm (hazard ratios were not reported). There were no differences in toxicity between arms. The study was terminated early and failed to reach accrual target. One underpowered trial (84 participants), which was closed early for slow accrual provided very low quality evidence comparing MVAC with carboplatin and paclitaxcel (CaP) (Dreicer et al., 2004). There were no differences between arms for overall survival and progression-free survival. Rates of neutropenia and anaemia were higher in the MVAC arm, but there were no differences in rates of thrombocytopenia and treatment-related mortality. It was reported that there were no differences in quality of life over time by treatment arm, but low numbers of participants were assessed for quality of life, which limits the precision of this outcome. One underpowered trial (110 participants) provided very low quality evidence of no difference in overall survival, time-to-progression, and toxicity between patients treated with Gemcitabine and Cisplatin versus Gemcitabine and Carboplatin (Dogliotti et al., 2007).

Four trials comparing cisplatin-based chemotherapy with carboplatin-based chemotherapy were included in the meta-analysis by Galsky et al. (2012). Very low quality evidence from two studies showed no difference in survival rate at 12 months (RR 0.76, 95% CI 0.56 to 1.07). Progression-free survival was not reported consistently across studies and could not be pooled in a meta-analysis. Therefore, overall tumour response rates and complete tumour response rates were pooled and risk ratios (95% CIs) were calculated. A partial tumour response was defined as a 50% reduction in bidimensional tumour measurements and a complete response as a resolution of radiographic abnormalities. A majority of patients had a performance status of 0 to 1 with adequate renal function. The meta-analysis demonstrated a higher likelihood of achieving an overall response (RR 1.34, 95% CI 1.04 to 1.71) and a complete response (RR 3.54, 95% CI 1.48 to 8.49) with cisplatin-based chemotherapy. However, this analysis is based on three small phase II studies and one phase III trial which was closed early due to poor accrual. The chemotherapy agents used and the doses of carboplatin used differed across studies.

Chemotherapy in 'unfit' patients

Moderate quality evidence for overall survival and progression-free survival was provided by one phase III RCT (238 participants) comparing Gemcitabine & Carboplatin (GCarbo) with Methotrexate & Carboplatin & Vinblastine (M-CAVI) (De Santis et al., 2012) in patients unfit for cisplatin-based therapy. After a median of 4.5 years follow-up there were no differences in overall survival (HR 0.94, 95% CI 0.72 to 1.02) and progression-free survival (HR 1.04, 0.8 to 1.35) between the two treatments. GCarbo produced a lower rate of severe acute toxicity than M-CAVI (9% vs. 21%). There were no differences between treatments for changes in health-related quality of life from baseline to end of cycle 2, although mean scores were not reported and there was less than 50% response rate after the baseline assessment.

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Table 99: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Cisplatin & Methotrexate (CM) versus Cisplatin (C)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CM	C	Relative (95% CI)	Absolute	Quality
Overall survival (follow-up range 2-5 years)											
1[1]	randomised trials	none	none	None	very serious[2]	none	N=53	N=55	HR not reported	Median OS, 8.7 months vs. 7.2 months[3]	LOW
Progression-free survival (follow-up 2-5 years)											
1[1]	randomised trials	none	none	None	very serious[2]	none	N=53	N=55	HR not reported	Median PFS, 5 months vs. 2.8 months[4]	LOW
Toxicity - Grade 3-4 Haematological											
1	randomised trials	none	none	None	very serious[2]	none	14/53 (26.4%)	4/55 (7.3%)	RR 3.63 (1.28 to 10.33)	191 more per 1000 (from 20 more to 679 more)	LOW
Toxicity - Grade 3-4 Mucositis											
1[1]	randomised trials	none	none	None	very serious[5]	none	10/53 (18.9%)	0/55 (0%)	RR 21.78 (1.31 to 362.56)	-	LOW
Toxicity - Grade 3-4 Nausea/Vomiting											
1[1]	randomised trials	none	none	None	very serious[5]	none	23/53 (43.4%)	14/55 (25.5%)	RR 1.70 (0.99 to 2.95)	178 more per 1000 (from 3 fewer to 496 more)	LOW
Treatment-related mortality											
1[1]	randomised trials	none	none	None	very serious[5]	none	2/53 (3.8%)	1/55 (1.8%)6	RR 2.08 (0.19 to 22.22)	20 more per 1000 (from 15 fewer to 386 more)	LOW
Health-related quality of life											
0	no evidence available										

[1] Hillcoat et al. (1989); [2] Small sample size/low number of events limit precision of this outcome; [3] Median overall survival was 8.7 months with CM, and 7.2 months with C (p=0.7). Number of events in each arm during follow-up was not reported. Hazard ratios were not reported; [4] Median time-to-progression was 5 months with CM, and 2.8 months with C (the log rank test was not significant, p=0.13, but the Wilcoxon test was significant, p=0.02). Hazard ratios not reported. By the end of the second year after randomisation 10% of patients in both arms remained progression free (no significant differences between arms); [5] Wide confidence intervals/low number of events limits the precision of this outcome; [6] One death on the C arm resulted from neutropenic sepsis following M therapy given after C treatment

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Table 100: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: MVAC (Methotrexate, Vinblastine, Doxorubicin & Cisplatin) versus Methotrexate & Cisplatin (MC)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MVAC	MC	Relative (95% CI)	Absolute	Quality
Overall survival											
0	no evidence available										
Progression-free survival											
0	no evidence available										
Toxicity - Grade 3-4 Leucopoenia											
1[1]	randomised trials	none	none	None	very serious[2]	none	2/14 (14.3%)	1/14 (7.1%)	RR 2.00 (0.20 to 19.62)	71 more per 1000 (from 57 fewer to 1000 more)	LOW
Toxicity - Grade 2-3 Thrombocytopenia (WHO criteria)											
1[1]	randomised trials	none	none	None	very serious[2]	none	2/14 (14.3%)	1/14 (7.1%)	RR 2.00 (0.2 to 19.62)	71 more per 1000 (from 57 fewer to 1000 more)	LOW
Toxicity - Anaemia (Hb loss >3g)											
1[1]	randomised trials	none	none	None	very serious[2]	none	1/14 (7.1%)	1/14 (7.1%)	RR 1.00 (0.07 to 14.45)	0 fewer per 1000 (from 66 fewer to 961 more)	LOW
Treatment-related mortality											
0	no evidence available										
Health-related quality of life											
0	no evidence available										

[1] Pizzocaro et al. (1991); [2] Small number of participants/events and wide confidence intervals reduces the precision of this outcome

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Table 101: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: CMV (Cisplatin, Methotrexate & Vinblastine) versus MV

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CMV	MV	Relative (95% CI)	Absolute	Quality
Overall survival (maximum follow-up 2 years)											
1[1]	randomised trials	none	none	None	serious[2]	none	108	106	HR 0.68 (0.51 to 0.9)	Median OS, 7 vs. 4.5 mo	MODERATE
Progression-free survival (maximum follow-up 2 years)											
1[1]	randomised trials	none	none	None	serious[2]	none	108	106	HR 0.55 (0.41 to 0.73)	Median PFS, 5.5 vs. 3 mo	MODERATE
Toxicity - Grade 3 leucopoenia or thrombocytopenia											
1[1]	randomised trials	none	none	None	serious[2]	none	5/108 (4.6%)	0/106 (0%)	RR 10.8 (0.6 to 192.89)	-	MODERATE
Toxicity - Neutropenic fever requiring hospital admission and i.v antibiotics											
1[1]	randomised trials	none	none	None	serious[2]	none	11/108 (10.2%)	2/106 (1.9%)	RR 5.40 (1.23 to 23.78)	83 more per 1000 (from 4 more to 430 more)	MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	None	serious[2]	none	5/108 (4.6%)	0/106 (0%)	RR 10.80 (0.6 to 192.89)	-	MODERATE
Health-related quality of life											
0	no evidence available										

[1] Mead et al. (1998); [2] Wide confidence intervals /low number of events limit the precision of this outcome

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Table 102: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: MVAC (Methotrexate, Vinblastine, Doxorubicin & Cisplatin) versus Cisplatin

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MVAC	Cisplatin	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate, median follow-up 19.7 months)											
1[1]	randomised trials	serious[2]	none	None	serious[3]	none	106/126 (84.1%)	115/120 (95.8%)	HR 0.61 (0.47 to 0.79)	Median OS, 12.5 vs. 8.2 mo	LOW
Progression-free survival (progression or death rate, median follow-up 19.7 months)											
1[1]	randomised trials	serious[2]	none	None	serious[3]	none	108/126 (85.7%)	113/120 (94.2%)	Unable to calculate HR	Median PFS, 10 vs. 4.3 mo	LOW
Toxicity - Grade 3-4 Anaemia											
1[1]	randomised trials	None	none	None	very serious[3]	none	1/126 (0.8%)	1/120 (0.8%)	RR 0.95 (0.06 to 15.06)	0 fewer per 1000 (from 8 fewer to 117 more)	LOW
Toxicity - Grade 3-4 Leucopoenia											
1[1]	randomised trials	None	none	None	very serious[3]	none	30/126 (23.8%)	1/120 (0.8%)	RR 28.57 (3.96 to 206.24)	230 more per 1000 (from 25 more to 1000 more)	LOW
Toxicity - Grade 3-4 Granulocytopenic fever											
1[1]	randomised trials	None	none	None	very serious[3]	none	13/126 (10.3%)	0/120 (0%)	RR 25.72 (1.55 to 427.99)	-	LOW
Toxicity - Grade 3-4 Mucositis											
1[1]	randomised trials	none	none	None	very serious[3]	none	21/126 (16.7%)	0/120 (0%)	RR 40.97 (2.51 to 668.86)	-	LOW
Treatment-related mortality											
1[1]	randomised trials	none	none	None	very serious[3]	none	5/126 (4%)	0/120 (0%)	RR 10.48 (0.59 to 187.51)	-	LOW
Health-related quality of life											
0	no evidence available										

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[1] Loehrer et al. (1992) / Saxman et al. (1997); [2]Number of participants ineligible for the study and included in the final analysis differ between reports by Loehrer et al. (1992) and Saxman et al. (1997). HR calculated from p-value and number of observed events reported in Loehrer et al. (1992); [3] Wide confidence intervals and/or low number of events limit the precision of this outcome

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Table 103: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: High-dose MVAC versus MVAC

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose MVAC	MVAC	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate, median follow-up 7.3 years)											
1[1]	randomised trials	none	none	None	serious[2]	none	101/134 (75.4%)	112/129 (86.8%)	HR 0.76 (0.58 to 0.99)3	Median OS, 15.1 vs. 14.9 mo	MODERATE
Progression-free survival (progression or death rate, median follow-up 7.3 years)											
1[1]	randomised trials	none	none	None	serious[2]	none	109/134 (81.3%)	116/129 (89.9%)	HR 0.73 (0.56 to 0.95)4	Median PFS, 9.5 vs. 8.1 mo	MODERATE
Toxicity - Grade 3-4 Whole blood cell (WBC) (WHO criteria)											
1[1]	randomised trials	none	none	None	serious[2]	none	27/134 (20.1%)	80/129 (62%)	RR 0.32 (0.23 to 0.47)	422 fewer per 1000 (from 329 fewer to 478 fewer)	MODERATE
Toxicity - Grade 3-4 Thrombocytopenia (WHO criteria)											
1[1]	randomised trials	none	none	None	serious[2]	none	28/134 (20.9%)	22/129 (17.1%)	RR 1.23 (0.74 to 2.03)	39 more per 1000 (from 44 fewer to 176 more)	MODERATE
Toxicity - Grade 3-4 Mucositis (WHO criteria)											
1[1]	randomised trials	none	none	None	serious[2]	none	13/134 (9.7%)	22/129 (17.1%)	RR 0.57 (0.3 to 1.08)	73 fewer per 1000 (from 119 fewer to 14 more)	MODERATE
Neutropenic fever											
1[1]	randomised trials	none	none	None	serious[2]	none	13/134 (9.7%)	33/129 (25.6%)	RR 0.38 (0.21 to 0.69)	159 fewer per 1000 (from 79 fewer to 202 fewer)	MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	None	serious[2]	none	1/134 (0.7%)	1/129 (0.8%)	RR 0.96 (0.06 to 15.23)	0 fewer per 1000 (from 7 fewer to 110 more)	MODERATE
Health-related quality of life											
0	no evidence available										

[1] Sternberg et al. (2001a/2006); [2] Wide confidence intervals/low number of events limit the precision of this outcome; [3] HR indicates mortality risk. 2-year overall survival rate was 37% (95% CI 28%-45%) for HD-MVAC and 26% (95% CI 18%-34%) for MVAC; [4] HR indicates progression risk. 2-year progression-free survival rate was 24.7% (95% CI 17.1% to 32.3%) for HD-MVAC versus 11.6% (95% CI 5.9% to 17.4%) for MVAC.

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Table 104: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Docetaxcel & Cisplatin (DC) with GCSF versus MVAC with GCSF

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	DC	MVAC	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate, median follow-up 25.3 months, range 3.2 to 51 months for surviving patients)											
1[1]	randomised trials	none	none	None	serious[2]	none	84/111 (75.7%)	74/109 (67.9%)	HR 1.52 (1.11 to 2.08)	Median OS, 9.3 vs. 14.2 mo	MODERATE
Progression-free survival (relapse rate during follow-up, median follow-up 25.3 months, range 3.2 to 51 months for surviving patients)											
1[1]	randomised trials	none	none	None	serious[2]	none	76/111 (68.5%)	65/109 (59.6%)	HR 1.73 (1.24 to 2.42)	Median TTP, 6.1 vs. 9.4 mo	MODERATE
Toxicity - Grade 3-4 Neutropenia (NCI Common Toxicity Criteria)											
1[1]	randomised trials	none	none	None	serious[2]	none	20/104 (19.2%)	37/103 (35.9%)	RR 0.54 (0.33 to 0.86)	165 fewer per 1000 (from 50 fewer to 241 fewer)	MODERATE
Toxicity - Grade 3-4 Thrombocytopenia (NCI Common toxicity criteria)											
1[1]	randomised trials	none	none	None	serious[2]	none	1/104 (1%)	6/103 (5.8%)	RR 0.17 (0.02 to 1.35)	48 fewer per 1000 (from 57 fewer to 20 more)	MODERATE
Toxicity - Grade 3-4 Anaemia (NCI Common toxicity criteria)											
1[1]	randomised trials	none	none	None	serious[2]	none	6/104 (5.8%)	8/103 (7.8%)	RR 0.74 (0.27 to 2.07)	20 fewer per 1000 (from 57 fewer to 83 more)	MODERATE
Toxicity - Grade 3-4 Neutropenic sepsis (NCI Common toxicity criteria)											
1	randomised trials	none	none	None	serious[2]	none	4/104 (3.8%)	12/103 (11.7%)	RR 0.33 (0.11 to 0.99)	78 fewer per 1000 (from 1 fewer to 104 fewer)	MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	None	serious[2]	none	1/111 (0.9%)	2/109 (1.8%)	RR 0.49 (0.05 to 5.34)	9 fewer per 1000 (from 17 fewer to 80 more)	MODERATE
Health-related quality of life											
0	no evidence available										

[1] Bamias et al. 2004; [2] Wide confidence intervals / low number of events limit the precision of this outcome

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Table 105: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine & Cisplatin (GC) versus MVAC

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate, maximum follow-up 5 years)											
1[1]	randomised trials	none	none	None	none	none	176/203 (86.7%)	171/202 (84.7%)	HR 1.09 (0.88 to 1.34)	Median OS, 14 vs. 15.2 mo	HIGH
Progression-free survival (progression or death rate, maximum follow-up 5 years)											
1[1]	randomised trials	none	none	None	none	none	184/203 (90.6%)	178/202 (88.1%)	HR 1.09 (0.89 to 1.34)	Median PFS, 7.7 vs. 8.3 mo	HIGH
Toxicity - Grade 3-4 anaemia (WHO criteria)											
1[1]	randomised trials	none	none	None	serious[2]	none	55/203 (27.1%)	36/202 (17.8%)	RR 1.52 (1.05 to 2.21)	93 more per 1000 (from 9 more to 216 more)	MODERATE
Toxicity - Grade 3-4 thrombocytopenia (WHO criteria)											
1[1]	randomised trials	none	none	None	serious[2]	none	116/203 (57.1%)	42/202 (20.8%)	RR 2.75 (2.02 to 3.69)	364 more per 1000 (from 212 more to 559 more)	MODERATE
Toxicity - Grade 3-4 neutropenia (WHO criteria)											
1[1]	randomised trials	none	none	None	None	none	144/203 (70.9%)	166/202 (82.2%)	RR 0.86 (0.77 to 0.96)	115 fewer per 1000 (from 33 fewer to 189 fewer)	HIGH
Neutropenic sepsis											
1[1]	randomised trials	none	none	None	serious[2]	none	2/203 (1%)	24/202 (11.9%)	RR 0.08 (0.02 to 0.35)	109 fewer per 1000 (from 77 fewer to 116 fewer)	MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	None	serious[2]	none	2/203 (1%)	5/202 (2.5%)	RR 0.40 (0.08 to 2.03)	15 fewer per 1000 (from 23 fewer to 25 more)	MODERATE
Health-related quality of life (measured with: EORTC quality of life questionnaire C30; Better indicated by higher values)											
1[1]	randomised trials	none	none	None	serious[2]	none	165	161	-	MD 0 higher (0 to 0 higher)[3]	MODERATE
Patient preferences for GC vs MVAC											
1[4]	observational	serious[5]	none	none	serious[2]	none			Not	-	VERY LOW

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Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute	Quality
	studies								estimable6		

[1] von der Maase et al. (2000/2005); [2] Low number of events limits precision; [3] Mean scores not reported. The authors state that quality of life was maintained on both arms throughout the study with both arms noting improvements in emotional functioning and pain. More GC-treated patients reported at least a 10 point improvement in fatigue compared to MVAC-treated patients (33% versus 28%). This difference was not statistically significant; [4] Aristides et al. (2005); [5] Number and characteristics of respondents not reported. Oncology professionals interviewed as patient representatives; [6] Respondents were almost eight times more likely to choose GC over MVAC for a reduced incidence of neutropenic sepsis (OR 7.7, 95% CI 3.0-17.8, p<0.001). Respondents were four times more likely to choose GC over MVAC for reduced incidence of mucositis (OR 4.1, 95% CI 1.9-9.0), or serious weight loss (OR 3.9, 95% CI 2.1-7.3) Overall, respondents were willing to accept GC over MVAC with a probability of 0.9972, given an equal life expectancy of 60 weeks. This significant probability remained despite a hypothetical reduction in life expectancy to 45 weeks for patients treated with GC

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Table 106: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Dose dense MVAC (DD-MVAC) versus Dose dense Gemcitabine & Cisplatin (DD-GC)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DD-MVAC	DD-GC	Relative (95% CI)	Absolute	Quality
Overall survival (follow-up median 52 months; assessed with: Mortality rate)											
1[1]	randomised trials	none	none	None	very serious[2]	none	45/63 (71.4%)	44/63 (69.8%)	Not reported p=0.98	-	LOW
Progression-free survival (follow-up mean 52.1 months)											
1[1]	randomised trials	none	none	None	very serious[2]	none	52/63 (82.5%)	47/63 (74.6%)	Not reported p=0.36	-	LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	None	very serious[2,3]	none	12/61 (19.7%)	8/59 (13.6%)	RR 1.45 (0.64 to 3.29)	61 more per 1000 (from 49 fewer to 311 more)	LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	None	very serious[2,3]	none	5/61 (8.2%)	5/59 (8.5%)	RR 0.97 (0.30 to 3.17)	3 fewer per 1000 (from 59 fewer to 184 more)	LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	None	very serious[2,3]	none	7/61 (11.5%)	6/59 (10.2%)	RR 1.13 (0.40 to 3.16)	13 more per 1000 (from 61 fewer to 220 more)	LOW
Grade 3-5 toxicities (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	None	very serious[2,3]	none	30/61 (49.2%)	26/59 (44.1%)	RR 1.12 (0.76 to 1.64)	53 more per 1000 (from 106 fewer to 282 more)	LOW
Treatment-related mortality											
1[1]	randomised trials	none	none	None	very serious[2,3]	none	2/63 (3.2%)	0/63 (0%)	RR 5.00 (0.24 to 102.10)	-	LOW
Health-related quality of life											
0	No evidence available										

[1] Bamias et al. (2013); [2] Low number of events. Underpowered study. Trial closed early due to poor accrual; [3] Wide confidence interval (includes null value) limits precision

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Table 107: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine & Cisplatin & Paclitaxel (PCG) versus Gemcitabine & Cisplatin (GC)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCG	GC	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate, follow-up median 4.6 years, maximum 6.8 years)											
1[1]	randomised trials	none	none	None	none	none	248/312 (79.5%)	256/314 (81.5%)	HR 0.85 (0.71 to 1.02)[2]	Median OS, 15.8 vs. 12.7 mo	HIGH
Overall survival - Bladder tumour (mortality rate, follow-up median 4.6 years)											
1[1]	randomised trials	none	none	None	none	none	198/254 (78%)	213/259 (82.2%)	HR 0.80 (0.66 to 0.97)[3]	Median OS, 15.9 vs. 11.9 mo	HIGH
Progression-free survival (progression or death rate, follow-up median 4.6 years)											
1[1]	randomised trials	none	none	None	none	none	269/312 (86.2%)	278/314 (88.5%)	HR 0.87 (0.74 to 1.03)	Median PFS = 8.3 vs. 7.6 mo	HIGH
Severe acute toxicity (NCI Common Toxicity Criteria)											
1[1]	randomised trials	none	none	None	serious[4]	none	61/302 (20.2%)	45/305 (14.8%)	RR 1.37 (0.96 to 1.94)	52 more per 1000 (from 6 fewer to 139 more)	MODERATE
Grade 3-4 Neutropenia											
1[1]	randomised trials	none	none	None	none	none	194/302 (64.2%)	154/305 (50.5%)	RR 1.27 (1.11 to 1.46)	136 more per 1000 (from 56 more to 232 more)	HIGH
Grade 3-4 Thrombocytopenia											
2[5]	randomised trials	none	none	None	none	none	119/345 (34.5%)	168/348 (48.3%)	RR 0.71 (0.6 to 0.86)	140 fewer per 1000 (from 68 fewer to 193 fewer)	HIGH
Grade 3-4 Anaemia											
1[6]	randomised trials	none	none	None	serious[4]	none	9/42 (21.4%)	10/43 (23.3%)	RR 0.92 (0.42 to 2.04)	19 fewer per 1000 (from 135 fewer to 242 more)	MODERATE
Treatment-related mortality											
1[1]	randomised trials	none	none	None	serious[4]	none	6/302 (2%)	3/305 (1%)	RR 2.02 (0.51 to 8)	10 more per 1000 (from 5 fewer to 69 more)	MODERATE

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Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCG	GC	Relative (95% CI)	Absolute	Quality
Health-related quality of life											
0	no evidence available										

[1] Bellmunt et al. (2012); [2] The overall survival rate at 1 year was 61.4% with PCG, and 52.8% with GC; [3] In the 81% of patients in whom bladder was the site of the primary tumour, median overall survival was 15.9 months with PCG and 11.9 months with GC (p=.025); [4] Wide confidence intervals limit the precision of this outcome; [5] Bellmuntet al. (2012); Lorusso et al. (2005); [6] Lorusso et al. (2005)

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Table 108: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: MVAC versus Carboplatin & Paclitaxcel (CaP)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MVAC	CaP	Relative (95% CI)	Absolute	Quality
Overall survival (follow-up median 32.5 months)											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none			Not estimable[3]	-	VERY LOW
Progression-free survival											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none			Not estimable[4]	-	VERY LOW
Toxicity - Grade 3 or higher neutropenia (NCI Common Toxicity Criteria)											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none	29/43 (67.4%)	12/41 (29.3%)	RR 2.30 (1.37 to 3.87)	380 more per 1000 (from 108 more to 840 more)	VERY LOW
Toxicity - Grade 3 or higher anaemia (NCI Common Toxicity Criteria)											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none	16/43 (37.2%)	2/41 (4.9%)	RR 7.63 (1.87 to 31.13)	323 more per 1000 (from 42 more to 1000 more)	VERY LOW
Toxicity - Grade 3 or higher thrombocytopenia (NCI Common Toxicity Criteria)											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none	9/43 (20.9%)	4/41 (9.8%)	RR 2.15 (0.72 to 6.43)	112 more per 1000 (from 27 fewer to 530 more)	VERY LOW
Treatment-related mortality											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none	1/43 (2.3%)	1/41 (2.4%)	RR 0.95 (0.06 to 14.75)	1 fewer per 1000 (from 23 fewer to 335 more)	VERY LOW
Health-related quality of life (follow-up 10 months; measured with: Functional Assessment of Cancer Therapy - Bladder; Better indicated by higher values)											
1[1]	randomised trials	very serious[2]	none	None	serious[6]	none	43	41	-	MD 0 higher (0 to 0 higher)[7]	VERY LOW

[1] Dreicer et al. 2004; [2] Underpowered trial - closed early because of slow accrual; [3] Numbers of patients alive at follow-up not reported, Hazard ratios not reported. Median overall survival was 15.4 months with MVAC, and 13.8 months with CaP (p=0.65); [4] Number of patients with disease progression not reported. Hazard ratios not reported. Median progression-free survival was 8.7 months with MVAC, and 5.2 months with CaP (p=0.24); [5] Wide confidence intervals, small sample size and/or low number of events limit the precision of this outcome; [6] Low number of participants assessed for quality of life at study entry (n=38) and at 10 month follow-up (n=14) which reduces the precision of this outcome; [7] Mean FACT-BL scores not reported - authors state there was no significant differences over time by treatment arm (p=0.33).

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Table 109: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine & Cisplatin (GC) versus Gemcitabine & Carboplatin (GCarbo)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	GC	GCarbo	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate, follow-up median 7 months)											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none	7/55 (12.7%)	7/55 (12.7%)	HR not reported	Median OS, 12.8 vs. 9.8 mo[3]	VERY LOW
Disease progression (follow-up median 7 months)											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none	NR	NR	HR not reported	Median TTP, 8.3 vs. 7.7 mo[4]	VERY LOW
Toxicity - Grade3-4 Neutropenia (WHO criteria)											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none	19/55 (34.5%)	25/55 (45.5%)	RR 0.76 (0.48 to 1.21)	109 fewer per 1000 (from 236 fewer to 95 more)	VERY LOW
Toxicity - Grade 3-4 Thrombocytopenia (WHO criteria)											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none	17/55 (30.9%)	22/55 (40%)	RR 0.77 (0.46 to 1.29)	92 fewer per 1000 (from 216 fewer to 116 more)	VERY LOW
Toxicity - Grade 3-4 Anaemia (WHO criteria)											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none	11/55 (20%)	14/55 (25.5%)	RR 0.79 (0.39 to 1.58)	53 fewer per 1000 (from 155 fewer to 148 more)	VERY LOW
Treatment-related mortality											
1[1]	randomised trials	very serious[2]	none	None	serious[5]	none	-	-	Not estimable[6]	-	VERY LOW
Health-related quality of life											
0	no evidence available										

[1] Dogliotti et al. 2007; [2] Underpowered trial, insufficient follow-up; [3] Median survival was 12.8 months with GC, and 9.8 months with GCarbo (reported by authors as not clinically significant, hazard ratios not provided); [4] Median time to progression was 8.3 months (range 7.5-9.1) with GC, and 7.7 (range 5.1-10.3) with GCarbo, (reported by authors as not significant, hazard ratios not provided); [5] Wide confidence intervals / low number of events limit the precision of this outcome; [6] 14 deaths reported in Dogliotti (2007), 13 were not considered drug related. 1 patient in the GC group died of acute renal failure possibly related to cisplatin. No toxicity data available for this patient because blood sample not collected.

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Table 110: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: MVAC versus M-CAVI (Methotrexate, Carboplatin, Vinblastine)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MVAC	M-CAVI	Relative (95% CI)	Absolute	Quality
Overall survival (disease-related mortality rate, follow-up median 18 months, range 6-60 months)											
1[1]	randomised trials	none	none	None	very serious[2]	none	19/24 (79.2%)	18/23 (78.3%)	HR 0.49 (0.26 to 0.93)	Median DSS, 16 vs. 9 months[3]	LOW
Progression-free survival											
0	no evidence available										
Toxicity - Grade 3-4 Stomatitis											
1[1]	randomised trials	none	none	None	very serious[2]	none	5/24 (20.8%)	1/23 (4.3%)	RR 4.79 (0.6 to 37.95)	165 more per 1000 (from 17 fewer to 1000 more)	LOW
Toxicity - Grade 3-4 Thrombocytopenia											
1[1]	randomised trials	none	none	None	very serious[2]	none	1/24 (4.2%)	1/23 (4.3%)	RR 0.96 (0.06 to 14.43)	2 fewer per 1000 (from 41 fewer to 584 more)	LOW
Toxicity - Grade 3-4 Anaemia											
1[1]	randomised trials	none	none	None	very serious[2]	none	1/24 (4.2%)	1/23 (4.3%)	RR 0.96 (0.06 to 14.43)	2 fewer per 1000 (from 41 fewer to 584 more)	LOW
Treatment-related mortality											
1[1]	randomised trials	none	none	None	very serious[2]	none	1/24 (4.2%)	0/23 (0%)	RR 2.88 (0.12 to 67.29)	-	LOW
Health-related quality of life											
0	no evidence available										

[1] Bellmunt et al. (1997); [2] Low number of participants/events and wide confidence intervals limits the precision of this outcome. HR calculated from p-value and observed number of events. [3] Median disease-related survival was 16 months (range 3 to 24+) for MVAC, and 9 months (range 2 to 17) for M-CAVI (p= 0.03).

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Table 111: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Cisplatin-based chemotherapy versus Carboplatin-based chemotherapy

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cisplatin-based	Carboplatin-based	Relative (95% CI)	Absolute	Quality
Overall survival (Mortality at 12 months)											
2[1]	randomised trials	very serious[2]	none	None	serious[3]	none	NR	NR	RR 0.775 (0.56 to 1.07)	-	VERY LOW
Progression-free survival											
0	no evidence available[4]										
Overall tumour response (partial+complete response, WHO definition)											
4[5]	randomised trials	very serious[2]	none	None	serious[3]	none	73/128 (57%)	54/128 (42.2%)	RR 1.34 (1.04 to 1.71)	143 more per 1000 (from 17 more to 300 more)	VERY LOW
Complete tumour response (WHO definition)											
4[5]	randomised trials	very serious[2]	none	None	serious[3]	none	23/128 (18%)	5/128 (3.9%)	RR 3.54 (1.48 to 8.49)	99 more per 1000 (from 19 more to 293 more)	VERY LOW
Toxicity											
4[5]	randomised trials	very serious[2]	none	None	None	none	-	-	Not estimable6	-	LOW
Health-related quality of life (follow-up 10 months; measured with: Functional Assessment of Cancer Therapy - Bladder; Better indicated by higher values)											
1[7]	randomised trials	very serious[2]	none	None	serious[8]	none	N=43	N=41	-	MD 0 higher (0 to 0 higher)[9]	VERY LOW

[1] Dreicer et al. (2004); Dogliotti et al. (2007); [2] Three of the included trials were closed early and were underpowered to detect clinically significant differences between arms; [3] Wide confidence intervals / low number of events limit the precision of this outcome; [4] Progression-free survival data could not be pooled; [5] 4 trials included in meta-analysis by Galsky et al. (2012) - Bellmunt et al. (1997); Dogliotti et al. (2007); Dreicer et al. (2004); Petrioli et al. (1996); [6] Toxicity data could not be pooled. Trials generally report more severe toxicity with Cisplatin-based regimens compared with Carboplatin-based regimens; [7] Dreicer et al. (2004); [8] Low number of participants assessed for quality of life at study entry (n=38) and at 10 month follow-up (n=14) which reduces the precision of this outcome; [9] Mean FACT-BL scores not reported - authors state there was no significant differences over time by treatment arm (p=0.33).

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Table 112: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine & Carboplatin (GCarbo) versus Methotrexate, Carboplatin & Vinblastine (M-CAVI) in patients unfit for cisplatin

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	GCarbo	M-CAVI	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate, follow-up median 4.5 years, maximum 7.8 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	110/119 (92.4%)	108/119 (90.8%)	HR 0.94 (0.72 to 1.02)	Median OS, 9.3 vs. 8.1 mo	MODERATE
Progression-free survival (progression or death rate, follow-up median 4.5 years, maximum 7.8 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	115/119 (96.6%)	113/119 (95%)	HR 1.04 (0.8 to 1.35)	Median PFS, 5.8 vs. 4.2 mo	MODERATE
Severe Acute Toxicity (SAT) (follow-up median 4.5 years; NCI-Common Toxicity Criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	11/118 (9.3%)	25/118 (21.2%)	RR 0.44 (0.23 to 0.85)	119 fewer per 1000 (from 32 fewer to 163 fewer)	MODERATE
Treatment-related mortality (follow-up median 4.5 years)											
1[1]	randomised trials	none	none	none	Serious[3]	none	3/119 (2.5%)	4/119 (3.4%)	RR 0.75 (0.17 to 3.28)	8 fewer per 1000 (from 28 fewer to 77 more)	MODERATE
Health-related quality of life (measured with: EORTC Quality of life questionnaire C30, measured until end of treatment; Better indicated by higher values)											
1[1]	randomised trials	none	none	none	Serious[4]	none	0	0	-	MD 0 higher (0 to 0 higher)[5]	MODERATE

[1] De Santis et al. (2012); [2] Low number of events limit precision; [3] Wide confidence intervals and low number of events suggest imprecise results; [4] Low compliance (90% at baseline and less than 50% afterward) limits the precision of this outcome. Mean scores for each arm across time not reported; [5] Authors state there were no differences between the two treatment arms for changes in primary scale global health status/QoL from baseline to end of cycle 2.

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Cost-effectiveness evidence

The primary results of the analysis by Robinson et al. 2004 are summarised in table 113.

The base case results of the cost-effectiveness analysis showed that, in comparison to the MVAC regimen, the combination of gemcitabine and cisplatin provided one additional quality adjusted life year (QALY) at a cost of £22,925. This ICER value is slightly higher than the threshold typically adopted by NICE (£20,000 per QALY) and so gemcitabine and cisplatin would not strictly be considered cost-effective.

Exceptions are made in instances where there may be some aspects that are not captured in the model. In this case, the cost of gemcitabine used in the model is unlikely to reflect the cost in current practice as the drug has come off patent in the intervening years. With the lower cost of gemcitabine in current practice, it is possible that the cost-effectiveness result would be improved significantly and could fall below the threshold of £20,000 per QALY.

However, there were concerns about the utility values that were used in the model as they were derived from healthcare professionals rather than patients and thus the QALY estimates may be unreliable. Furthermore, the applicability of this study to current practice is debatable as the MVAC regimen used in the study has largely been replaced with a more efficacious accelerated MVAC regimen.Thus, overall, the available evidence base was not considered to provide a reliable estimate of cost-effectiveness that is relevant to current clinical practice.

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Table 113: Modified GRADE table showing the included evidence on the optimal first-line chemotherapy regimens for treating metastatic bladder cancer

Study	Population	Comparators: initial diagnosis (follow-up)	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Robinson et al. 2004	Patients with locally advanced or metastatic bladder cancer.	Methotrexate / vinblastine / doxorubicin / cisplatin (MVAC)	Base case estimate: £9,633	Not reported	Reference standard			One-way sensitivity analyses were conducted on unit cost and length of stay parameters by varying original values by ±25%. The authors concluded that the model was robust to these changes. The authors considered the uncertainty shown in the CI calculations to be the only major source of uncertainty within the model. Probabilistic sensitivity analysis (PSA) was not conducted.	Partly applicable. The evaluation considers the UK health system. However, the utility values were not directly reported by patients (as recommended by NICE). Instead they were elicited from healthcare professionals.	Potentially serious limitations. Potential conflict of interest as the study was funded by Eli Lilly and Co, the manufacturer of one of the therapies under consideration (Gemcitabine). In addition, further sensitivity analysis could have been conducted to better explore uncertainty. .
		Gemcitabine / cisplatin (GC)	Base case estimate: £12,609	Not repored	Base case estimate: £2,976 Unfavourable (Upper) CI estimate: £3,526 Favourable (lower) CI estimate: £2,427	Base case estimate: 0.130 QALYs Unfavourable (lower) CI estimate: 0.105 QALYs Favourable (upper) CI estimate: 0.188 QALYs	Base case estimate: £22,925 per QALY Unfavourable CI estimate: £33,589 per QALY Favourable CI estimate: £12,911 per QALY			
	Comments: The analysis was an atypical health economic evaluation because a decision analytic model was not constructed. Instead, the authors combined the results of a costing analysis based on a clinical trial with a parallel cross-sectional utility study.									

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Recommendations	**Discuss the role of first-line chemotherapy with people who have locally advanced or metastatic bladder cancer. Include in your discussion:** • **prognosis of their cancer and** • **advantages and disadvantages of the treatment options, including best supportive care.** **Offer a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine, or accelerated [high-dose] methotrexate, vinblastine, doxorubicin and cisplatin [M-VAC] in combination with granulocyte-colony stimulating factor [G-CSF]) to people with locally advanced or metastatic urothelial bladder cancer who are otherwise physically fit (have an Eastern Cooperative Oncology Group [ECOG] performance status of 0 or 1) and have adequate renal function (typically defined as a glomerular filtration rate [GFR] of 60 ml/min/1.73 m^2 or more).** **Offer carboplatin in combination with gemcitabine[h] to people with locally advanced or metastatic urothelial bladder cancer with an ECOG performance status of 0 - 2, if a cisplatin-based chemotherapy regimen is unsuitable, for example, because of ECOG performance status, inadequate renal function (typically defined as a GFR of less than 60 ml/min/1.73 m^2) or comorbidity. Assess and discuss the risks and benefits with the person.** **For people having first-line chemotherapy for locally advanced or metastatic bladder cancer:** • **carry out regular clinical and radiological monitoring and** • **actively manage symptoms of disease and treatment-related toxicity and** • **stop first-line chemotherapy if there is excessive toxicity or disease progression.**
Relative value placed on the outcomes considered	All the outcomes specified in the PICO were reported in the evidence. The GDG considered progression-free survival, overall survival, and toxicity as the most important outcomes. Improvements in these outcomes were considered the most meaningful endpoints for patients/patient care. Survival is threatened by metastatic or locally advanced disease and overall prognosis is poor. Therefore, significant improvement in survival associated with chemotherapy treatment is considered to be an important outcome. Chemotherapy treatments have toxic adverse events so the GDG considered regimens delivering lower levels of toxicity. Tumour response was not specified in the PICO but was reported in the systematic review of cisplatin versus non-cisplatin based chemotherapy (Galsky, 2012) as no other outcomes could be pooled. Tumour response was considered by the GDG as a surrogate outcome for treatment effectiveness.
Quality of the evidence	The evidence ranged from low to high quality across comparisons as

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

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	assessed with GRADE. The GDG considered the limitation of the post-hoc analysis of overall survival for the subgroup of bladder tumours in the PCG trial (Bellmunt, 2012). Post-hoc selections can introduce bias. Less weight was placed on the positive outcome reported in the PCG trial due to these limitations. In light of this concern, PCG was recommended as an option to consider because the GDG did not believe the evidence warranted recommending offering this treatment as the best option. The recommendation that patients should be carefully monitored for toxicity was based on clinical experience. No specific evidence on how to monitor patients was examined, although all included trials stopped treatment if patients progressed or if there was excessive toxicity. The GDG reached consensus that treatment options, including the use of chemotherapy and best supportive care should be discussed with the patient. The GDG considered making a research recommendation for a trial of GC versus HDMVAC but considered this unlikely to be funded or to have sufficient support to take forward. Low quality health economic evidence was identified. The economist highlighted a potential bias in that it was a manufacturer sponsored study. Other limitations of the study include the cost of drug was not included in sensitivity analysis, utility data was not reported directly from patients, drug costs have changed since analysis conducted (come off patent),the comparator of MVAC is outdated (HDMVAC is now more widely used). The GDG therefore considered the economic analysis to be of limited value to current practice.
Trade-off between clinical benefits and harms	The main benefits of the recommendations made are that they provide clear guidance for patients to be offered chemotherapy and for which patient groups cisplatin-based chemotherapy is appropriate. This should improve outcomes for patients in terms of overall and progression-free survival. The recommendations made may increase the use of cisplatin-based chemotherapy and therefore increased toxicity and adverse effects may be expected. The GDG considered survival to be more important than toxicity and that patients are likely to consider the survival advantage and toxicity when deciding on treatment. The GDG considered that the potential for increased toxicity is mitigated by recommending the careful monitoring of patients for adverse events and discontinuing treatment if there is excessive toxicity. There was weak evidence to suggest a benefit of doublet chemotherapy as second line chemotherapy, when indirectly compared with best supportive care or single agent chemotherapy. The GDG therefore recommended doublet chemotherapy be considered. The GDG considered making a ‘do not offer’ recommendation for single agent chemotherapy, but decided after extensive discussion and following stakeholder feedback that there was insufficient evidence to make a

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	recommendation either way.
Trade-off between net health benefits and resource use	The GDG considered that the economic evidence identified was not applicable to current practice and no economic model was built. The potential costs of the recommendations made include the increased use of chemotherapy and GCSF. The potential savings include the avoidance of ineffective chemotherapy and possibly the avoidance or delay of the costs of palliative care. Improved survival means that chemotherapy is potentially cost-effective in cost/QALY terms.
Other considerations	The GDG considered that the recommendations equalise access to treatment for patients who currently don't have access. Patients who are both suitable and unsuitable for cisplatin-based chemotherapy are accounted for in recommendations. The GDG considered that the implementation of these recommendations would not cause a significant change in current practice.

6.1.2 Second-line chemotherapy

Management options for people who progress on or relapse after first line treatment are controversial. Their prognosis is poor with median survivals measured in a few months. There is a wide variety of practice in whether to offer second line therapy to such people. It is likely that response rates are less; and toxicity may be higher thus questioning the clinical benefits of treatment. A key question is first therefore whether there is a role for further chemotherapy in some or all of these people? If so, can the people that are most likely to benefit be identified, therefore allowing treatment to be avoided in those for whom chemotherapy is ineffective?

Clinical question: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

Clinical evidence (see also full evidence review)

The evidence is summarised in tables 114 to 142.

Evidence Statements

Single-agent chemotherapy

Very low quality evidence about the effectiveness of Topotecan, Iritonecan, Lapatanib, Sorefanib, Oxaliplatin and Sunitinib was provided by one non-comparative phase II study for each regimen. Overall survival ranged from 4.2 months (Lapatanib) to 7.1 months (Sunitinib). Progression-free survival ranged from 1.5 months (Topotecan) to 2.4 months (Sunitinib). Overall tumour response rate was highest for Topotecan at 9%. Toxicity rates were highest for Topotecan with 43%, 61%, and 77% of participants developing grade 3-4 thrombocytopenia, anaemia, and leucopenia, respectively. Two studies (46 participants) provided very low quality evidence on Bortezomib, with median overall survival durations of 3.5 months (Gomez-Aubin *et al.*, 2007) and 5.7 months (Rosenberg *et al.*, 2008). Both studies were closed early due to a lack of tumour response to the treatment, with no responses reported in either study. One study (47 participants) provided very low quality evidence of Pemetrexed, with a median overall survival of 9.2 months and a response rate of 28% for those previously treated in the metastatic setting (Sweeny *et al.*, 2006). A second smaller study (13 participants) of Pemetrexed reported a lower response rate of 8% (Galsky *et al.*, 2007). Across both studies, 12% of participants reported grade 3-4 neutropenia and thrombocytopenia. Very low quality evidence about the effectiveness of Gemcitabine was provided by four studies (133 participants), with overall survival ranging from 5 months to 13 months across studies and an overall tumour response of 22%. Grade 3-4 neutropenia was

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the most common adverse event (37% of participants) (2 studies, 79 participants). In one study (Albers *et al.*, 2002), 25 participants reported health-related quality of life, where responders to Gemcitabine showed an improvement in pain score from 4.3 to 5.8 on a 7-point scale. In contrast, non-responders reported an increase in pain during treatment.

Multi-agent chemotherapy

The combination of Gemcitabine and Paclitaxel (GP) was reported by 6 non-comparative observational studies (109 participants, very low quality evidence). The overall response rate was 30%, with median overall survival ranging from 8 months to 12.4 months. One study reported a median progression-free survival of 6.1 months (Ikeda *et al.*, 2011). Four studies reported grade 3-4 neutropenia, with an overall rate of 42%. One randomised phase III trial (Albers *et al.*, 2011) and one randomised phase II trial (Fechner *et al.*, 2006) provided low quality evidence of short-term (three-week schedule) versus prolonged (maintenance until progression) GP regimes (123 participants). No differences in overall survival and progression-free survival were reported between trial arms. In the phase III trial median overall survival was 7.8 months in the subgroup of patients who had first-line chemotherapy for metastatic cancer (Albers *et al.*, 2011). The pooled overall tumour response rate was 41% in both trial arms. Grade 3-4 leucopenia was the most common toxicity with no difference in rate between short-term and maintenance GP treatment (36% versus 23%). Two treatment-related deaths were reported on the prolonged GP arm in the phase III study. Several small non-randomised studies providing very low quality evidence, generally show that other non-platinum based regimens (e.g. Methotrexate & Paclitaxel; Paclitaxel & Ifosfamide; Docetaxel & Ifosfamide; Docetaxel & Oxaliplatin; Gemcitabine & Ifosfamide; Gemcitabine & Docetaxel) have lower response rates and overall survival durations than Gemcitabine and Paclitaxel.

Three studies (93 participants) reported very low quality evidence about Carboplatin and Paclitaxel, with median overall survival ranging from six to 11 months, and an overall response rate of 25%. Progression-free survival was around four months in all three studies. Grade 3-4 neutropenia was reported in 50 out of 93 (54%) participants. Health-related quality of life was reported by one study, where there were no differences between pre-treatment and post-treatment scores on the EORTC-QLQ C30. Cisplatin based multi-agent chemotherapy regimens (MVAC; Gemcitabine & Cisplatin (GC); Paclitaxel, Methotrexate & Cisplatin (PMC); Paclitaxel & Cisplatin; Cisplatin, Gemcitabine & Ifosfamide) produced response rates of 30% to 40% and overall survival durations of 9.5 to 11 months (very low quality evidence). Rates of grade 3-4 neutropenia were 30%-67% and rates of grade 3-4 thrombocytopenia were 30%-32% for MVAC, GC and PMC. Lower toxicity rates were reported for the regimen of Paclitaxel & Cisplatin, with 5% grade 3-4 neutropenia and 1% grade 3-4 thrombocytopenia and anaemia (Uhm *et al.*, 2007). One study (26 participants, very low quality evidence) reported a median overall survival and progression-free survival of 12.6 months and 5 months with Gemcitabine, Carboplatin & Docetaxel (Tsuruta *et al.*, 2011). Excluding those who had received combination radiation therapy, the overall tumour response rate was 56%. Toxicity data were not reported separately for patients receiving second-line chemotherapy. Grade 3-4 neutropenia was reported in 80% of participants, thrombocytopenia in 51%, and anaemia in 43%. There were no treatment-related deaths.

Best supportive care

Moderate quality evidence came from the control arm of a phase III randomised trial which reported a median overall survival of 4.6 months and a median progression-free survival of 1.5 months for 117 participants receiving best supportive care for progression after first-line chemotherapy (Bellmunt *et al.*, 2009). There were no tumour responses. One patient reported grade 3-4 neutropenia and one patient reported grade 3-4 thrombocytopenia. Nine participants reported grade 3-4 anaemia. Health-related quality of life as measured by the EORTC QLQ-C30, decreased continuously from baseline through to week 18 (mean scores were not reported).

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Table 114: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Topotecan for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topotecan**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=44	-	Median OS=6.3 months		VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=44	-	Median PFS=1.5 months		VERY LOW
Overall tumour response (assessed with: ECOG criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	4/44[3] (9.1%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia											
0[1]	No evidence available										
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	19/44 (43.2%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	27/44 (61.4%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	34/44 (77.3%)	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	0/44 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence										

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Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topotecan	Control	Relative (95% CI)	Absolute	Quality
	available										

[1] *Witte et al. 1997;* [2] *Small sample size and low number of events limits the precision of this outcome;* [3] *All partial responses, no complete responses*

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Table 115: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Iritonecan for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iritonecan	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=40	-	Median OS=5.4 months		VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=40	-	Median PFS=2.1 months		VERY LOW
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	none	serious[2]	none	2/40 (5%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia											
1[1]	observational studies	none	none	none	serious[2]	none	7/40 (17.5%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia											
1[1]	observational studies	none	none	none	serious[2]	none	2/40 (5%)	-	-	-	VERY LOW
Grade 3-4 Anaemia											
1[1]	observational studies	none	none	none	serious[2]	none	2/40 (5%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia											
1[1]	observational studies	none	none	none	serious[2]	none	5/40 (12.5%)	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	0/40 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Beer et al. 2008; [2] Small sample size and low number of events limits the precision of this outcome

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Table 116: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Lapatanib for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lapatanib	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=59	-	Median OS=4.2 months		VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=59	-	Median PFS=2 months		VERY LOW
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	none	serious[2]	none	1/59 (1.7%)	-	-	-	VERY LOW
Any adverse event (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	54/59 (91.5%)[3]	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	5/59 (8.5%)[4]	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Wulfing et al. 2009; [2] Small sample size and low number of events limit the precision of this outcome; [3] The most common grade 3 and/or 4 adverse events were vomiting (7%), diarrhoea (3%), dehydration (3%), and hyponatremia (3%); [4] Five patients died from serious adverse events: febrile neutropenia, cardiac arrest, enterostomy suture leakage, metastatic neoplasm, exacerbated dyspnea

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Table 117: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Bortezomib for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bortezomib	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	N=46	-	Median OS = 3.5 and 5.7 months		VERY LOW
Progression-free survival											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	N=46	-	Median PFS = 1.4 and 2 months		VERY LOW
Overall tumour response (assessed with: RECIST)											
2[1]	observational studies	none	none	serious[2]	None	none	0/46 (0%)	-	-	-	
Grade 3-4 Neutropenia (assessed with: NCI-CTCAE)											
1[4]	observational studies	none	none	None	serious[3]	none	0/24 (0%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	1/46 (2.2%)	-	-	-	VERY LOW
Grade 3-4 Anaemia											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	2/46 (4.3%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTCAE)											
1[4]	observational studies	none	none	none	serious[3]	none	0/24 (0%)	-	-	-	VERY LOW
Treatment-related mortality											
0[1]	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Rosenberg et al. 2008, Gomez-Abuin et al. 2007 [2] Adjuvant and neoadjuvant chemotherapy considered as first-line therapy in Gomez-Abuin et al. 2007 (40% of sample) [3] Small sample size limits the precision of this outcome [4] Rosenberg et al. 2008

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Table 118: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Sorafenib for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sorafenib	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=22	-	Median OS=6.8 months		VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=22	-	Median PFS=2.2 months		VERY LOW
Overall tumour response (assessed with: RECIST)											
1	observational studies	none	none	none	serious[2]	none	0/22 (0%)	-	-	-	VERY LOW
Toxicity (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	0/22 (0%)[3]	-	-	-	VERY LOW
Grade 4 pulmonary embolism (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	2/22 (9.1%)	-	-	-	VERY LOW
Grade 3 fatigue (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	5/22 (22.7%)	-	-	-	VERY LOW
Grade 3 hand-foot reaction (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	5/22 (22.7%)	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	0/22 (0%)	-	-	-	VERY LOW

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sorafenib**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Health-related quality of life											
0	No evidence available										

[1] Dreicer et al. 2009 [2] Small sample size and low number of events limit precision of outcome [3] Toxicity data not fully reported. Authors state that "Toxicity from sorafenib was similar to that seen in a renal cancer population".

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Table 119: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Oxaliplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxaliplatin	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=20	-	Median OS=7 months		VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=20	-	Median PFS=1.5 months		VERY LOW
Overall tumour response (assessed with: WHO criteria)											
1[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	1/20 (5%)	-	-	-	VERY LOW
Grade 3-4 Haematological toxicity (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	0/22 (0%)[3]	-	-	-	VERY LOW
Grade 3 Fatigue (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	4/20 (20%)	-	-	-	VERY LOW
Grade 3 Nausea (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	2/20 (10%)	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	1/20 (5%)[4]	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Winquist et al. 2005 [2] Small sample size and low number of events limits the precision of this outcome [3] No haematological toxicity above grade 2 was seen. No symptomatic neutropenia. [4] One treatment-related death from pulmonary embolism

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Table 120: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Pemetrexed for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pemetrexed	Control	Relative (95% CI)	Absolute	Quality
Overall survival (follow-up median 9.2 months)											
1[1]	observational studies	none	none	none [2]	serious[3]	none	N=29	-	Median OS = 9.2 months		VERY LOW
Progression-free survival (follow-up median 9.2 months)											
1[1]	observational studies	none	none	serious[4]	serious[3]	none	N=47	-	Median PFS = 2.9 months		VERY LOW
Overall tumour response (assessed with: SWOG / RECIST criteria)											
2[5]	observational studies	none	none	serious[6]	serious[3]	none	9/41 (22%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
2[5]	observational studies	none	none	serious[4]	serious[3]	none	7/60 (11.7%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
2[5]	observational studies	none	none	serious[4]	serious[3]	none	7/60 (11.7%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
2[5]	observational studies	none	none	serious[4]	serious[3]	none	4/60 (6.7%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia											
1[1]	observational studies	none	none	serious[4]	serious[3]	none	1/47 (2.1%)	-	-	-	VERY LOW
Treatment-related mortality											
2[5]	observational studies	none	none	serious[4]	serious[3]	none	0/60 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Sweeny 2006; [2] Neoadjuvant and adjuvant chemotherapy considered as first-line therapy. Median overall survival was reported separately for patients treated in the metastatic setting (n=29) [3] Small sample size/low number of events limits the precision of this outcome; [4] Progression-free survival and toxicity was not reported separately for patients who received prior neoadjuvant/adjuvant chemotherapy and those treated in the metastatic setting [5] Galsky et al. 2007, Sweeny 2006; [6] Tumour response was not reported separately for patients who received prior neoadjuvant/adjuvant chemotherapy and those treated in the metastatic setting in Galsky et al. 2007

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Table 121: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Docetaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Docetaxel**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival											
2[1]	observational studies	none	none	serious[2]	serious[5]	none	N=102	-	Median OS =9 and 7.3 months		VERY LOW
Progression-free survival											
1[3]	observational studies	none	none	serious[2]	serious[5]	none	N=72	-	Median PFS = 1.58 months		VERY LOW
Overall tumour response											
2[1]	observational studies	none	none	serious[2]	serious[5]	none	12/102 (11.8%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
2[1]	observational studies	none	none	serious[2]	serious[5]	none	35/102 (34.3%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[4]	observational studies	none	none	serious[2]	serious[5]	none	1/30 (3.3%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
2	observational studies	none	none	serious[2]	serious[5]	none	9/102 (8.8%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia											
0	No evidence available										
Treatment-related mortality											
1[3]	observational studies	none	none	serious[2]	serious[5]	none	0/72 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Choueiri et al. 2012, McCaffrey et al. 1997; [2] Neoadjuvant and adjuvant chemotherapy considered as first-line chemotherapy in both studies [3] Choueiri et al. 2012; [4] McCaffrey et al. 1997 [5] Small sample size/low number of events limits the precision of this outcome

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Table 122: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Ifosfamide for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ifosfamide	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
2[1]	observational studies	none	none	none	serious[2]	none	N=86	-	Median OS = 8 and 5.5 months		VERY LOW
Progression-free survival											
2[1]	observational studies	none	none	none	serious[2]	none	N=86	-	Median PFS = 6 and 2.5 months		VERY LOW
Overall tumour response (assessed with: ECOG/WHO criteria)											
2[1]	observational studies	none	none	none	serious[2]	none	12/76 (15.8%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia											
0	No evidence available										
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[3]	observational studies	none	none	none	serious[2]	none	12/56 (21.4%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[2]	observational studies	none	none	none	serious[2]	none	23/56 (41.1%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia											
1[2]	observational studies	none	none	none	serious[2]	none	36/56 (64.3%)	-	-	-	VERY LOW
Treatment-related mortality											
2[1]	observational studies	none	none	none	serious[2]	none	4/76 (5.3%)[4]	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Pronzato et al. 1997, Witte et al. 1997; [2] Small sample size/low number of events limits the precision of this outcome [3] Witte et al. 1997 (no grade 3-4 hematologic toxicities were reported by Pronzato et al. (1997) which may be due to differences in the dosing schedule of Ifosfamide used, therefore toxicity data were not pooled); [4] Four early deaths were reported by Witte et al. 1997, which although could not be directly linked to treatment, it was assumed treatment was a contributing factor

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Table 123: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Sunitinib for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sunitinib Cohort A**	**Sunitinib Cohort B**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=45	N=32	Median OS = 7.1 vs. 6.0 months (p=0.4)		VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=45	N=32	Median PFS = 2.4 vs.2.3 months (p=0.4)		VERY LOW
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	3/45 (6.7%)	1/32 (3.1%)	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/45 (2.2%)	3/32 (9.4%)	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	9/45 (20%)	3/32 (9.4%)	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	7/45 (15.6%)	4/32 (12.5%)	-	-	VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	2/45 (4.4%)	3/32 (9.4%)	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/45 (2.2%)	0/32 (0%)	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Gallagher et al. 2010; [2] Neoadjuvant and adjuvant chemotherapy (39% of sample) considered as first-line chemotherapy [3] Small sample size/low number of events limits the precision of this outcome

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Table 124: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Paclitaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paclitaxel	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	N=76	-	Median OS = 7.2 and 6.5 months		VERY LOW
Progression-free survival											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	N= 76	-	Median PFS = 2.2 and 3 months		VERY LOW
Overall tumour response (assessed with: RECIST)											
2[4]	observational studies	none	none	serious[2]	serious[3]	none	7/76 (9.2%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
2[5]	observational studies	none	none	serious[2]	serious[3]	none	3/74 (4.1%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[6]	observational studies	none	none	serious[2]	serious[3]	none	0/30 (0%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
2[1]	observational studies	none	none	serious[2]	serious[3]	none	9/74 (12.2%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Health-related quality of life (assessed with: Improvement in at least 1 domain (≥+5 points) FACT-G, FACT bl, FACT-Taxane)											
1[7]	observational studies	none	none	serious[2]	serious[3]	none	6/35 (17.1%)[8]	-	-	-	VERY LOW

[1] Vaughn et al. 2002, Joly et al. 2009; [2] Neoadjuvant and adjuvant chemotherapy considered as first-line chemotherapy; [3] Small sample size/low number of events suggest imprecise outcome [4] Vaughn et al. 2002, Joly et al. 2009. Papamichael et al (1997) was not included in the pooled analysis due to different dosage schedules used. Overall response rate reported by Papamichael et al (1997) was 4/14 (29%) compared to 9% (Joly et al. 2009) and 10% (Vaughn et al. 2002) [5] Vaughn et al. 2002, Joly et al. 2009. Papamichael et al 1997 was not included in the pooled analysis due to different dosage schedules used and toxicity data were not reported consistently. Papamichael reported that grade 3-4 hematologic toxicity was seen in 23/42 (55%) courses; [6] Vaughn et al. 2002; [7] Joly et al. 2009; [8] There was no decrease in the different QoL domains during chemotherapy

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Table 125: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
4[1]	observational studies	none	none	serious[2]	serious[8]	none	N=133 [3]	-	-	-	VERY LOW
Progression-free survival											
3[4]	observational studies	none	none	serious[2]	serious[8]	none	N=119 [5]	-	-	-	VERY LOW
Overall tumour response (assessed with: WHO criteria)											
4[1]	observational studies	none	none	serious[2]	serious[8]	none	28/127 (22%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia											
2[6]	observational studies	none	none	serious[2]	serious[8]	none	29/79 (36.7%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia											
4[1]	observational studies	none	none	serious[2]	serious[8]	none	11/131 (8.4%)	-	-	-	VERY LOW
Grade 3-4 Anaemia											
4[1]	observational studies	none	none	serious[2]	serious[8]	none	16/131 (12.2%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia											
4[1]	observational studies	none	none	serious[2]	serious[8]	none	29/131 (22.1%)	-	-	-	VERY LOW
Treatment-related mortality											
1[7]	observational studies	none	none	serious[2]	serious[8]	none	0/44 (0%)	-	-	-	
Health-related quality of life (measured with: Spitzer pain index; Better indicated by lower values)											
1[9]	observational studies	none	none	serious[2]	serious[8]	none	25[10]	-	-		VERY LOW

[1] Lorusso et al. 1998, Albers et al. 2002, Gebbia et al. 1999, Akaza et al. 2007; [2] Adjuvant and neoadjuvant chemotherapy considered as first-line chemotherapy; [3] Median overall survival ranged from 5 months to 13 months across studies; [4] Lorusso et al. 1998, Albers et al. 2002, Akaza et al. 2007; [5] Median progression-free survival ranged from 3.1 months to 4.9 months; [6] Lorusso et al. 1997, Akaza et al. 2007; [7] Akaza et al. 2007 [8] Small sample size and/or low number of events limit the precision of this outcome; [9] Albers et al. 2002; [10] Non-responders showed a decrease in pain values from 5.3 to 4.8 which corresponds to an increase in pain during treatment. Responders showed an improvement in pain values from 4.3 to 5.8 (p<0.05).

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Table 126: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine & Paclitaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine, paclitaxel	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
4[1]	observational studies	none	none	none	serious[13]	none	N=92 [2]	-	-	-	VERY LOW
Progression-free survival (follow-up median 20.4 months)											
1[3]	observational studies	none	none	serious[4]	serious[13]	none	N=24 [5]	-	-	-	VERY LOW
Overall tumour response (assessed with: RECIST/WHO criteria)											
6[6]	observational studies	none	none	none	serious[13]	none	33/109 (30.3%)[7]	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
4[1]	observational studies	none	none	none	serious[13]	none	50/118 (42.4%)[8]	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
4[1]	observational studies	none	none	none	serious[13]	none	10/92 (10.9%)[9]	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
3[10]	observational studies	none	none	none	serious[13]	none	5/68 (7.4%)[11]	-	-	-	VERY LOW
Grade 3-4 Leucopenia											
0	No evidence available										
Treatment-related mortality											
41	observational studies	none	none	none	serious[13]	none	1/92 (1.1%)[12]	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Sternberg 2001b, Kanai et al. 2008, Suyama et al. 2009, Ikeda et al. 2011; [2] Median overall survival reported were 8 months (Sternberg 2001b), 11.3 months (Suyama et al. 2009),11.5 months (Kanai et al. 2008), and 12.4 months (Ikeda et al. 2011). Takahashi et al. (2006) reported a median overall survival of 12.1 months, but this included patients receiving both first-line and second-line GP chemotherapy; [3] Ikeda 2011 [4] Neoadjuvant and adjuvant chemotherapy considered first-line therapy. Proportion of participants not reported; [5] Median progression-free survival was 6.1 months; [6] Kaufman 2004, Sternberg 2001b, Takahashi et al. 2006, Kanai et al. 2008, Suyama et al. 2009, Ikeda et al. 2011; [7] Overall tumour response rate ranged from 17% to 42% across studies; [8] Rate of grade 3-4 neutropenia ranged from 30% to 67% across studies; [9] Rates of grade 3-4 thrombocytopenia ranged from 0% to 29% across studies; [10] Sternberg 2001b, Kanai et al. 2008, Suyama et al. 2009; [11] Rates of grade 3-4 anaemia ranged from 0% to 15% [12] One treatment related death reported by Sternberg 2001b; [13] Small sample size/low number of events reduces precision

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Table 127: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Short-term versus prolonged gemcitabine and paclitaxel

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-term GP	Prolonged GP	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate, minimum follow-up 5 years)											
1[1]	randomised trials	none	none	serious[2]	serious[5]	none	47/48 (97.9%)	46/48 (95.8%)	HR 0.94 (0.63 to 1.41)[3]	Median OS, 7.8 vs. 8 months	LOW
Progression-free survival											
2[7]	randomised trials	none	none	serious[2]	serious[5]	none	N=62	N=61	Unable to calculate HR4	-	LOW
Overall tumour response (assessed with: RECIST criteria)											
2[7]	randomised trials	none	none	serious[2]	serious[5]	none	22/54 (40.7%)	22/54 (40.7%)	RR 1.00 (0.63 to 1.58)	0 fewer per 1000 (from 151 fewer to 236 more)	LOW
Grade 3-4 Thrombocytopenia (assessed with: WHO criteria)											
1[6]	randomised trials	none	none	serious[2]	serious[5]	none	0/14 (0%)	2/13 (15.4%)	RR 0.13 (0.01 to 2.36)	134 fewer per 1000 (from 152 fewer to 209 more)	LOW
Grade 3-4 Anaemia (assessed with: WHO/NCI criteria)											
2[7]	randomised trials	none	none	serious[2]	serious[5]	none	5/54 (9.3%)	14/54 (25.9%)	RR 0.42 (0.17 to 1.03)	150 fewer per 1000 (from 215 fewer to 8 more)	LOW
Grade 3-4 Leucopenia (assessed with: WHO criteria)											
1[6]	randomised trials	none	none	serious[2]	serious[5]	none	5/14 (35.7%)	3/13 (23.1%)	RR 1.55 (0.46 to 5.22)	127 more per 1000 (from 125 fewer to 974 more)	LOW
Treatment-related mortality											

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Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Short-term GP**	**Prolonged GP**	**Relative (95% CI)**	**Absolute**	
1[1]	randomised trials	none	none	serious[2]	serious[5]	none	0/40 (0%)	2/41 (4.9%)	RR 0.20 (0.01 to 4.14)	39 fewer per 1000 (from 48 fewer to 153 more)	LOW
Health-related quality of life											
0	No evidence available					none	-	-	-	-	

[1] Albers et al. 2011; [2] Adjuvant and neoadjuvant chemotherapy considered as first-line chemotherapy (56% of sample in Albers 2011, 67% of sample in Fechner et al. 2006); [3] HR calculated from Albers et al. (2011). Insufficient data from Fechner (2006). Median overall survival was 13 months with short-term GP, and 9 months with prolonged GP (Fechner et al. 2006). Median OS was 7.8 months in the subgroup of patients who had first-line chemotherapy for metastatic cancer (Albers et al. 2011); [4] No significant differences between trial arms were reported. Median progression-free survival was 11 months (Fechner et al. 2006) and 4 months (Albers et al. 2011) with short-term GP, and 6 months (Fechner et al. 2006) and 3.1 months (Albers et al. 2011) with prolonged GP; [5] Small sample size/low number of events and/or wide confidence intervals suggest imprecise outcome; [6] Fechner et al. 2006; [7] Albers et al. 2011; Fechner et al. 2006

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Table 128: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Paclitaxel & Carboplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carboplatin, paclitaxel	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	N=933	-	-	-	VERY LOW
Progression-free survival											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	N=934	-	-	-	VERY LOW
Overall tumour response (assessed with: RECIST/WHO criteria)											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	23/93 (24.7%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	50/93 (53.8%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	7/93 (7.5%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
3[1]	observational studies	none	none	serious[2]	serious[6]	none	23/93 (24.7%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTC)											
1[5]	observational studies	none	none	serious[2]	serious[6]	none	16/44 (36.4%)	-	-	-	VERY LOW
Treatment-related mortality											
2[7]	observational studies	none	none	serious[2]	serious[6]	none	1/75 (1.3%)[8]	-	-	-	VERY LOW
Health-related quality of life (follow-up 3 months; assessed with: EORTC-QLQ C30)											
1[9]	observational studies	none	none	serious[2]	serious[6]	none	1510	-	-	-	VERY LOW

[1] Kouno et al. 2007, Vaishampayan et al. 2005, Soga et al. 2007; [2] Neoadjuvant and adjuvant chemotherapy considered as first-line chemotherapy in all studies; [3] Median overall survival reported = 6 months, 7.9 months and 11 months (Vaishampayan et al. 2005, Kouno et al. 2007, Soga et al. 2007); [4] Median progression-free survival = 3.7 months, 4 months and 4 months (Kouno et al. 2007, Vaishampayan et al. 2005, Soga et al. 2007) [5] Vaishampayan et al. 2005; [6] Small sample size/low number of events limits the precision of this outcome; [7] Kouno et al. 2007, Vaishampayan et al. 2005; [8] One patient with a PS score of 3 died due to neutropenic sepsis (Kouno et al. 2007). No further PS3 patients were recruited; [9] Soga et al. 2007; [10] There were no differences between pre-treatment and post-treatment data on all scales of the EORTC QLQ C30

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Table 129: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MVAC	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=30	-	Median OS = 10.9 months		VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	none	serious[2]	none	N=30	-	Median PFS = 5.3 months		VERY LOW
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	none	serious[2]	none	9/30 (30%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	19/30 (63.3%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	9/30 (30%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	5/30 (16.7%)	-	-	-	VERY LOW
Grade 3-4 Mucositis (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	4/30 (13.3%)	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	0/30 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Han et al. 2008 [2] Small sample size/low number of events limits the precision of this outcome

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Table 130: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine, cisplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gemcitabine, cisplatin**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=33	-	Median OS = 10.5 months		VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	13/33 (39.4%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	22/33 (66.7%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	10/33 (30.3%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	14/33 (42.4%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	15/33 (45.5%)	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/33 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Gondo et al. 2011 [2] Adjuvant MVAC considered as first-line MVAC chemotherapy [3] Small sample size/ low number of events limit the precision of this outcome

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Table 131: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Paclitaxel, cisplatin, methotrexate for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paclitaxel, methotrexate, cisplatin	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
0	No evidence available										
Progression-free survival											
0	No evidence available										
Overall tumour response											
1[1]	observational studies	none	none	none	serious[2]	none	10/25 (40%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: ECOG criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	9/25 (36%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: ECOG criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	8/25 (32%)	-	-	-	VERY LOW
Significant nephrotoxicity (assessed with: >50% serum creatinine increase)											
1[1]	observational studies	none	none	none	serious[2]	none	6/25 (24%)	-	-	-	VERY LOW
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] *Tu et al. 1995* [2] *Small sample size/ low number of events limit the precision of this outcome*

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Table 132: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Paclitaxel, cisplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paclitaxel, cisplatin**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival (follow-up median 16.4 months)											
1[1]	observational studies	none	none	none	serious[2]	none	N=28	-	Median OS = 10.3 months		VERY LOW
Progression-free survival (follow-up median 16.4 months)											
1[1]	observational studies	none	none	none	serious[2]	none	N=28	-	Median PFS = 6.2 months		VERY LOW
Overall tumour response (assessed with: WHO criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	10/28 (35.7%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	5/110 (4.5%)[3]	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	1/110 (0.91%)[3]	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[3]	none	1/110 (0.91%)[3]	-	-	-	VERY LOW
Grade 3-4 Emesis (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	10/28 (35.7%)[4]	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	none	serious[2]	none	0/28 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Uhm et al. 2007 [2] Small sample size / low number of events limit the precision of this outcomes [3] Toxicity rate reported per cycle of chemotherapy [4] Toxicity rate reported per patient

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Table 133: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Methotrexate, paclitaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Methotrexate, paclitaxel**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=20	-	Median OS = 5 months		VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	6/20 (30%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	3/20 (15%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/20 (0%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/20 (5%)	-	-	-	VERY LOW
Grade 3 Mucositis (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/20 (5%)	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/20 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available					none	-	-	-	-	

[1] Bellmunt et al. 2002 [2] Neoadjuvant chemotherapy considered as first-line chemotherapy [3] Small sample size / low number of events limit the precision of this outcome

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Table 134: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Paclitaxel, ifosfamide for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paclitaxel, ifosfamide**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=13	-	Median OS = 8 months		VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	2/13 (15.4%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	4/13 (30.8%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia											
1	observational studies	none	none	serious[2]	serious[3]	none	2/13 (15.4%)	-	-	-	VERY LOW
Grade 3-4 Anaemia											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/13 (7.7%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia											
0	No evidence available										
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/13 (7.7%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Sweeny et al. 1999 [2] Adjuvant and neoadjuvant chemotherapy considered as first-line chemotherapy (proportion of sample not stated) [3] Small sample size/ low number of events limit the precision of this outcome

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Table 135: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Docetaxel, ifosfamide for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Docetaxel, ifosfamide**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=22	-	Median OS = 4 months		VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	5/20 (25%)	-	-	-	VERY LOW
Neutropenic sepsis (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/22 (4.5%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/22 (4.5%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/22 (0%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia (assessed with: WHO criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	11/53 (20.8%)[4]	-	-	-	VERY LOW
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Krege et al. 2001; [2] Neoadjuvant (n=2) and adjuvant (n=4) chemotherapy considered as first-line chemotherapy; [3] Small sample size / low number of events limit the precision of this outcome[4] Reported as per cycle

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Table 136: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Docetaxel, oxaliplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Docetaxel, oxaliplatin	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=11	-	Median OS = 7 months		VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/11 (9.1%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/11 (0%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/11 (0%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/11 (0%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/11 (0%)	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/11 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Srinivas et al. 2009; [2] Adjuvant chemotherapy considered as first-line chemotherapy (55% of sample); [3] Small sample size / low number of events limit the precision of this outcome. Trial stopped early due to low response to therapy.

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Table 137: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Cisplatin, Gemcitabine & Ifosfamide for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cisplatin, gemcitabine, ifosfamide**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=51	-	Median OS = 9.5 months		VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: complete or partial response for 2 months)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	20/49 (40.8%)	-	-	-	VERY LOW
Febrile Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	2/51 (3.9%)	-	-	-	VERY LOW
Dose limiting hematologic toxicity (assessed with: NCI-CTC - any grade 4 toxicity or persistent >grade 2 toxicity)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	48/51 (94.1%)[4]	-	-	-	VERY LOW
Treatment-related mortality											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	1/51 (2%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Pagliaro et al. 2002; [2] Adjuvant (20%) and neoadjuvant (4%) chemotherapy considered as first-line chemotherapy; [3] Small sample size / low number of events limit the precision of this outcome [4] 100% dose omission on either day 8 or day 15 occured in virtually every course given, all due to granulocytopenia, thrombocytopenia or both

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Table 138: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine, Ifosfamide for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine, ifosfamide	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
2[1]	observational studies	none	none	none	serious[2]	none	N=57	-	Median OS = 4.8 and 9 months		VERY LOW
Progression-free survival											
2[1]	observational studies	none	none	none	serious[2]	none	N=57	-	Median PFS = 3.5 and 4 months		VERY LOW
Overall tumour response (assessed with: WHO criteria)											
2[1]	observational studies	none	none	none	serious[2]	none	12/57 (21.1%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: WHO criteria)											
1[3]	observational studies	none	none	none	serious[2]	none	9/34 (26.5%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: WHO/ECOG criteria)											
2[1]	observational studies	none	none	none	serious[2]	none	12/57 (21.1%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: WHO/ECOG criteria)											
2[1]	observational studies	none	none	none	serious[2]	none	11/57 (19.3%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia (assessed with: ECOG criteria)											
14	observational studies	none	none	none	serious[2]	none	10/23 (43.5%)	-	-	-	VERY LOW
Treatment-related mortality											
1[3]	observational studies	none	none	none	serious[2]	none	0/34 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Lin et al. 2007, Pectasides et al. 2001; [2] Small sample size / low number of events limit the precision of this outcome; [3] Pectasides et al. 2001; [4] Lin et al. 2007

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Table 139: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine, Docetaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gemcitabine, docetaxel**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=29	-	Median OS = 7.7 months		VERY LOW
Progression-free survival											
0	No evidence available										
Overall tumour response (assessed with: ECOG criteria)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	5/27 (18.5%)	-	-	-	VERY LOW
Neutropenic fever											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	2/29 (6.9%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	4/29 (13.8%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	8/29 (27.6%)	-	-	-	VERY LOW
Grade 3-4 Granulocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	10/29 (34.5%)	-	-	-	VERY LOW
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] Dreicer et al. 2003; [2] Adjuvant and neoadjuvant chemotherapy considered as first-line chemotherapy (proportion of sample not stated); [3] Small sample size / low number of events limit the precision of this outcome

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Table 140: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine, carboplatin, docetaxel for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gemcitabine, carboplatin, docetaxel	Control	Relative (95% CI)	Absolute	Quality
Overall survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=26	-	Median OS = 12.6 months		VERY LOW
Progression-free survival											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	N=26	-	Median PFS = 5 months		VERY LOW
Overall tumour response (assessed with: RECIST)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	9/16 (56.3%)[4]	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2,5]	serious[3]	none	28/35 (80%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2,5]	serious[3]	none	18/35 (51.4%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2,5]	serious[3]	none	15/35 (42.9%)	-	-	-	VERY LOW
Treatment-related mortality (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	serious[2]	serious[3]	none	0/35 (0%)	-	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Tsuruta et al. 2011; [2] Neoadjuant and adjuvant chemotherapy considered as first-line chemotherapy; [3] Small sample size / low number of events limit the precision of this outcome [4] Excluded participants who received combination radiation therapy; [5] Toxicity data not reported separately for 2nd line chemotherapy patients

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Table 141: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Methotrexate, Paclitaxel, Epirubicin, Carboplatin for second-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MPEC	Control	Relative (95% CI)	Absolute	Quality
Overall survival (median (range) follow-up: 14 (3-45) months)											
1[1]	observational studies	none	none	none	serious[2]	none	Median OS 12.5 months	-	-	-	VERY LOW
Progression-free survival (median (range) follow-up: 14 (3-45) months)											
1[1]	observational studies	none	none	none	serious[2]	none	Median PFS 12 months	-	-	-	VERY LOW
Overall tumour response rate (assessed with: WHO criteria)											
1[1]	observational studies	none	none	none	serious[2]	none	15/38 (39.5%)	-	-	-	VERY LOW
Grade 3-4 Neutropenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	12/40 (30%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	1/40 (2.5%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	observational studies	none	none	none	serious[2]	none	2/40 (5%)	-	-	-	VERY LOW
Treatment-related mortality											
0	No evidence available										
Health-related quality of life											
0	No evidence available										

[1] *Halim et al. (2013)* [2] *Low number of events/small sample size limits precision*

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Table 142: GRADE evidence profile: What is the optimal post first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Best supportive care after progression from first-line chemotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Best supportive care	Control	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate at follow-up)											
1[1]	randomised trials	none	none	none	serious[2]	none	103/117 (88%)	-	Median OS = 4.6 months		MODERATE
Progression-free survival											
1[1]	randomised trials	none	none	none	serious[2]	none	N=117	-	Median PFS = 1.5 months		MODERATE
Overall tumour response (assessed with: RECIST)											
1[1]	randomised trials	none	none	none	serious[2]	none	0/117 (0%)	-	-	-	MODERATE
Grade 3-4 Neutropenia (assessed with: NCI- CTC)											
1[1]	randomised trials	none	none	none	serious[2]	none	1/117 (0.85%)	-	-	-	MODERATE
Grade 3-4 Thrombocytopenia (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	none	serious[2]	none	1/117 (0.85%)	-	-	-	MODERATE
Grade 3-4 Anaemia (assessed with: NCI-CTC)											
1[1]	randomised trials	none	none	none	serious[2]	none	9/117 (7.7%)	-	-	-	MODERATE
Health-related quality of life											
1[1]	randomised trials	none	none	none	serious[2]	none	-[3]	-	-	-	MODERATE

[1] Bellmunt et al. 2009; [2] Low number of events reduces precision of this outcome; [3] Mean scores not reported. There was a continuous decrement in quality of life scores from baseline through week 18. 24% receieved at least one palliative radiotherapy treatment

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Discuss second-line chemotherapy with people who have locally advanced or metastatic bladder cancer. Include in your discussion:** • **the prognosis of their cancer** • **advantages and disadvantages of treatment options, including best supportive care.** **Consider second-line chemotherapy with gemcitabine in combination with cisplatin, or accelerated (high-dose) M-VAC in combination with G-CSF for people with incurable locally advanced or metastatic urothelial bladder cancer whose condition has progressed after first-line chemotherapy if:** • **their renal function is adequate (typically defined as a GFR of 60 ml/min/1.73 m^2 or more) and** • **they are otherwise physically fit (have an ECOG performance status of 0 or 1).** **Consider second-line chemotherapy with carboplatin in combination with paclitaxel[i] or gemcitabine in combination with paclitaxel[j] for people with incurable locally advanced or metastatic urothelial bladder cancer for whom cisplatin-based chemotherapy is not suitable, or who choose not to have it.** **For recommendations on vinflunine as second-line chemotherapy for people with incurable locally advanced or metastatic urothelial bladder cancer, see NICE's technology appraisal guidance on vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract.** **For people having second-line chemotherapy for locally advanced or metastatic bladder cancer:** • **carry out regular clinical and radiological monitoring and** • **actively manage symptoms of disease and treatment-related toxicity and** • **stop second-line chemotherapy if there is excessive toxicity or disease progression.**
Relative value placed on the outcomes considered	All outcomes from the PICO were reported in the evidence. Overall survival, progression-free survival, toxicity and quality of life were considered by the GDG to be the most important outcomes.

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

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

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	Quality of life and toxicity were considered very important for patients with a poor prognosis. Improving survival and time without further progressions would also be important aims of second line chemotherapy. Tumour response was not specified as an outcome in the PICO but was reported in the evidence review. This outcome had some influence in making the recommendation to not offer single agent chemotherapy because of the poor tumour response rates with single-agent treatments.
Quality of the evidence	The evidence was assessed as being of very low quality using GRADE. The evidence was limited by consisting of mostly small single arm studies. Additionally, only the control arm of the Vinflunine randomised trial could be considered by the GDG. The lack of any high quality evidence meant that only weak recommendations could be made in relation to specific chemotherapy regimens. No recommendations were based solely on clinical experience. The GDG considered a recommendation on re-challenging with first-line chemotherapy but decided against it because there was no strong evidence. The GDG recognised that second-line chemotherapy may be associated with lower response rates and higher toxicity and felt a recommendation/warning regarding careful monitoring and management was important. The GDG reached consensus that treatment options, including the use of chemotherapy and best supportive care should be discussed with the patient. A research recommendation was made because there is a lack of randomised trial data in this area and high unmet need. The GDG felt that it was important to offer guidance on the best available data but that further evidence might strengthen future recommendations and improve patient outcomes.
Trade-off between clinical benefits and harms	The potential benefits of the recommendations made include improved outcomes for patients in terms of survival and quality of life, providing clinicians with some guidance where there has been none previously, and reducing treatment variation. The recommendations may increase the use of second-line chemotherapy which may lead to increased toxicity for patients. The GDG considered survival to be more important than toxicity and that patients are likely to consider the survival advantage and toxicity when making decisions about treatment. The GDG considered that the potential for increased toxicity is mitigated by recommending the careful monitoring of patients for adverse events and discontinuing treatment if there is excessive toxicity.
Trade-off between net health benefits and resource use	No economic evidence was identified and no economic model was developed for this topic. The main cost of the recommendation is from the potential increase in the use of chemotherapy. The potential savings include the avoidance of ineffective chemotherapy and possibly the avoidance or delay of the costs of palliative care. The GDG considered that improved survival means that chemotherapy is potentially cost-

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	effective in cost/QALY terms.
Other considerations	The GDG considered that the recommendations equalise access to treatment for patients who currently don't have access. Patients who are both suitable and unsuitable for cisplatin-based chemotherapy are accounted for in recommendations. The GDG considered that there may be some increase chemotherapy use in places that don't currently use second-line chemotherapy. The GDG were also aware of the NICE TA 272 on Vinflunine and that there is the potential for a reduction in the use of single-agent chemotherapy outside of a clinical research study.

Research recommendation	**In patients with incurable locally advanced or metastatic bladder cancer after first line chemotherapy what is the most effective second line therapy (including single agent, combination therapy, novel agents or best supportive care).**
Why is this important	Many people with progressive bladder cancer after 1st line systemic chemotherapy do not have access to further treatment. As this group of These people are often unwell and have troublesome symptoms, and discussions about choices of anti-cancer treatments will be complex. The evidence upon which to base these decisions is poor with a single randomised phase III trial reporting only marginal benefits. High quality evidence is needed to inform consideration of the benefits and burdens of any chemotherapy interventions. This evidence will need to address not only the survival benefits of individual or combination therapies, but more importantly when to use them, for which individuals, and in what circumstances, these different interventions may or not may be effective.

6.2 Managing symptoms of locally advanced or metastic bladder cancer

6.2.1 Bladder symptoms

Radiotherapy can be used to help people with symptoms of incurable bladder cancer. It is sometimes given at the time of diagnosis but may be deferred and used when people are symptomatic. It is most commonly used to treat bleeding from the bladder or pain from the bladder cancer itself or sites of spread. Radiotherapy is also used to improve local control rates in people with advanced pelvic disease. Side-effects are related to the area treated but are usually well-tolerated and include short term urinary frequency and discomfort or diarrhoea and nausea.

The total dose and fractionation of radiotherapy varies across the UK.

Clinical question: What is the optimal pelvic radiotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

Clinical evidence (see also full evidence review)

The evidence is summarised in tables 143 to 145.

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Evidence statements

Moderate quality evidence about the relative effectiveness of two hypofractionated radiotherapy schedules (35 Gy in 10 fractions over two weeks versus 21 Gy in 3 fractions over one week) for local symptom control of muscle invasive bladder cancer came from one randomised trial (Duchesne *et al.*, 2000). 500 patients were randomised with three month follow-up data available in 272 patients. Overall symptom improvement, defined as improvement of at least one symptom by one grade without worsening another symptom, was 71% in those receiving 35-Gy compared with 64% in the 21-Gy arm, though there is uncertainty about thedifference between treatments (absolute improvement 3%, 95% CI -6% to 12%). Comparing the 35 Gy group with the 21 Gy group for patients with specific pre-treatment symptoms, urinary frequency resolved in 43% and 42%, respectively, nocturia in 51% and 35%, haematuria in 58% and 61%, and dysuria in 47% and 49%. Median survival was 7.5 months in both groups. Two-thirds of participants reported that quality of life symptom scores were either unchanged or improved by the end of treatment and at three months after treatment.

One observational study (Srinivasan *et al.*, 1994) provided low quality evidence about the relative effectiveness of hypofractionated (two-fraction) radiotherapy and conventional palliative radiotherapy in 41 patients selected by performance status. 59% of those receiving two-fraction radiotherapy had clearance of haematuria compared to 16% of those receiving conventional palliation (RR 3.74, 95% CI 1.25 to 11.19). Pain improved in 73% of those treated with two-fraction radiotherapy compared to 37% of those treated with conventional palliation (RR 1.97, 95% CI 1.04 to 3.75). All patients died during follow-up. Mean survival was 9.77 and 14.47 months in the hypofractionated and conventional radiotherapy groups respectively.

Very low quality evidence was reported from seven observational studies using various palliative radiotherapy regimens. Median survival ranged from six to nine months across studies. Complete palliation of symptoms was achieved in 51% of 65 elderly patients treated with 30 Gy in five fractions on a weekly basis, although 28 patients experienced transient worsening of their urinary symptoms with eight requiring hospital admission due to toxicities (McLaren *et al.*, 1997). Jose *et al.* (1999) reported on a similar radiotherapy schedule with control of haematuria in 50%, frequency in 63%, dysuria 38%, and nocturia 5%. This study also reported toxicity rates of 36% for acute bowel and 63% for acute bladder toxicity. One study of short-term radiotherapy (7Gy 3 times or 5Gy 4 times) reported that none of the 17 patients with severe local symptoms improved after radiotherapy, although improvement was difficult to assess as 10 of these patients died within four months (Holmang *et al.*, 1995). Haematuria was present in 14 patients but it continued in only two after radiotherapy. Another study of short-term radiotherapy (Wijkstrom *et al.*, 1991) reported an improvement in tumour associated symptoms in 75/162 (46%) patients, although 42% had various minor acute side effects and over half the population were treated for tumours considered to be curable. Five-year survival in patients considered to be curable was 21%, compared to 6% in patients treated for bleeding and 0% for patients with other local symptoms.

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Table 143: GRADE evidence profile: What is the optimal pelvic radiotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Palliative radiotherapy – 35Gy in 10 fractions versus 21Gy in 3 fractions

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**35 Gy-10**	**21 Gy-3**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall symptomatic improvement, Pre-treatment to end of treatment (improvement of at least one symptom by one grade without worsening of any other)											
1[1]	randomised trials	none	none	none	serious[2]	none	120/225 (53.3%)	115/232 (49.6%)	RR 1.08 (0.90 to 1.29)	3% (95% CI -6% to 12%)	MODERATE
Overall symptomatic improvement, Pre-treatment to 3-month assessment (improvement of at least one symptom by one grade without worsening of any other)											
1[1]	randomised trials	none	none	none	serious[2]	none	95/133 (71.4%)	89/139 (64%)	RR 1.12 (0.95 to 1.32)	7% (95% CI -2% to 13%)	MODERATE
Overall mortality											
1[1]	randomised trials	none	none	none	none	none	204/248 (82.3%)	198/252 (78.6%)	RR 1.05 (0.96 to 1.14)	Median survival 7.5 months in both arms	HIGH
Progression-free survival											
0	No evidence					none	-	-	-	-	
Treatment-related mortality											
0	No evidence					none	-	-	-	-	
Quality of life (patient reported symptoms) (assessed with: Rotterdam Symptom Checklist)											
1[1]	randomised trials	none[3]	none	none	serious[2]	none	-	-	-	No difference in change of any symptom between arms[4]	MODERATE

[1] Duchesne et al. (2000) [2] Low number of events limits precision [3] A high proportion of patients did not contribute information at the 3-month assessment due to death or deteriorating health. However, the reasons for missing data were similar between arms. [4] Over 2/3 of patients contributing data noted no change or improvement in their QoL by the end of treatment and at 3 months. QoL symptoms were generally better at 3-months than post-treatment.

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Table 144: GRADE evidence profile: What is the optimal pelvic radiotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Hypofractionated radiotherapy versus conventional palliative radiotherapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypofractionated RT	Conventional RT	Relative (95% CI)	Absolute	Quality
Clearance of haematuria											
1[1]	observational studies	serious[2]	none	none	serious[3]	none	13/22 (59.1%)	3/19 (15.8%)	RR 3.74 (1.25 to 11.19)	433 more per 1000 (from 39 more to 1000 more)	VERY LOW
Clearance or improvement of haematuria (assessed with: Stopped completely or haematuria but without hospitalisation)											
1[1]	observational studies	serious[2]	none	none	serious[3]	none	19/22 (86.4%)	13/19 (68.4%)	RR 1.26 (0.89 to 1.79)	178 more per 1000 (from 75 fewer to 541 more)	VERY LOW
Relief or improvement in pain (assessed with: Opiates discontinued or at least a 50% reduction in opiate requirement)											
1[1]	observational studies	serious[4]	none	none	serious[3]	none	16/22 (72.7%)	7/19 (36.8%)	RR 1.97 (1.04 to 3.75)	357 more per 1000 (from 15 more to 1000 more)	VERY LOW
Overall mortality rate											
1[1]	observational studies	serious[2]	none	none	serious[3]	none	22/22 (100%)	19/19 (100%)	-	Mean OS 9.77 versus 14.47 months in favour of conventional RT	VERY LOW
Progression-free survival											
0	No evidence										
Treatment-related mortality											
0	No evidence										
Treatment-related morbidity											
0	No evidence										
Quality of life											
0	No evidence										

[1] Srinivasan et al. (1994); [2] Patients selected for treatments based on performance status. Hypofractionated group were older and with poor performance status (WHO grade 4 or more) [3] Low number of events/small sample size limits precision; [4] No pain data for 7 (17%) patients

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Table 145: GRADE evidence profile: What is the optimal pelvic radiotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Palliative radiotherapy for bladder cancer (observational studies)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Palliative radiotherapy	Control	Relative (95% CI)	Absolute	Quality
Symptom control (complete relief or improvement of symptoms e.g. haematuria, frequency)											
7[1]	observational studies	serious[2]	none	none	serious[3]	none	43%-51% across studies	-	-	-	VERY LOW
Overall survival											
7[4]	observational studies	serious[2]	none	none	serious[3]	none	Median OS 6 to 9 months across studies	-	-	-	VERY LOW
Progression-free survival											
2[5]	observational studies	None	none	none	serious[3]	none	Median PFS 8.3 months to 14 months	-	-	-	VERY LOW
Treatment-related mortality											
1[6]	observational studies	None	none	none	serious[3]	none	5/96 (5.2%)	-	-	-	VERY LOW
Treatment-related morbidity (acute urinary or GI toxicity)											
7[1]	observational studies	serious[2]	none	none	serious[3]	none	Around 1/3 to 2/3 of patients reported acute toxicity across studies	-	-	-	VERY LOW
Quality of life											
0	No evidence available										

[1] Jose et al. (1999); McLaren et al. (1997); Holmang & Borghede (1996); Salminen (1992); Wijkstrom et al. (1991); Spagnoletti et al. (2010); Kouloulias et al. (2013) [2] In Jose et al. (1999) outcomes not reported separately for patients treated for local control and those treated for palliation. For all studies - outcome data not available for all patients due to poor health and high mortality rates. Length of follow-up not reported. [3] Small sample size and low number of events in each study limits precision, [4] Jose (1999); McLaren et al. (1997); Holmang & Borghede(1996); Salminen (1992); Wijkstrom et al. (1991); Spagnoletti et al. (2010); Saunders & Kiltie (2006) [5] Salminen et al. (1992); Kouloulias et al. (2013) [6] Holmang & Borghede (1996)

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer palliative hypofractionated radiotherapy to people with symptoms of haematuria, dysuria, urinary frequency or nocturia caused by advanced bladder cancer that is unsuitable for potentially curative treatment.**
Relative value placed on the outcomes considered	The following outcomes were considered by the GDG to be the most important: • Progression free survival • Overall survival • Treatment-related mortality • Treatment related morbidity • Symptom control (haematuria/pelvic pain/urinary frequency) • Health-related quality of life, inc patient reported outcomes All of the above were considered important outcomes because they impact upon patient well-being. The outcome of treatment-related mortality was specified in the PICO but was not reported in the evidence.
Quality of the evidence	The quality of the evidence was very low to high as assessed with GRADE. There were some limitations of the observational evidence presented. For example, one of the comparative studies was biased in that it was not randomised and patients were selected for treatment based on performance status. However, the low quality observational data was superseded by a UK randomised trial and the recommendation was based on this evidence. No health economic evidence was identified.
Trade-off between clinical benefits and harms	The GDG considered that the main clinical benefits of the recommendation include the relief of symptoms (such as pain and dysuria), potential prolonged local disease control, and reduction in hospital admissions due to uncontrolled symptoms, enabling patients to spend more time at home. These benefits were balanced against the potential harm from increased radiation related toxicity. The randomised trial reported that quality of life in patients receiving radiotherapy was neutral or improved, which suggests that benefits outweigh the harms. Toxicity was short lived and the GDG prioritised improvement of symptoms.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG considered the potential increased costs from more patients

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	receiving radiotherapy, which were balanced against the potential savings resulting from reduced hospital admissions and other palliative treatments, a reduction in the length of radiotherapy treatment, and fewer cystoscopies.
Other considerations	The GDG considered that the recommendations promote equality of access to radiotherapy for older patients. The GDG considered that very little change in practice is required in terms of the technique of radiotherapy but that there may be a modest increase in the number of patients (particularly elderly patients) referred for radiotherapy. The GDG debated making a recommendation on hypofractionated radiotherapy for asymptomatic patients but felt the evidence was not strong enough to support this recommendation either positively or negatively. The GDG also considered making a research recommendation to assess hypofractionated radiotherapy but it was not considered to be feasible.

6.2.2 Loin pain and symptoms of renal failure

In people with locally advanced bladder cancer, with or without metastases, the cancer can sometimes obstruct one or both ureters. If only one kidney is obstructed, the opposite kidney can often maintain normal kidney function. Here the decision to intervene is often based on whether the person has symptoms, such as loin pain, or whether optimal kidney function is essential e.g to enable safe administration of systemic chemotherapy.

However if both kidneys are obstructed, then kidney failure will occur and may be fatal if untreated. Fortunately, this is not common. One option is to manage kidney failure conservatively with no intervention. However, the obstruction can be relieved though, either by a urologist inserting a retrograde stent, or by a radiologist inserting a nephrostomy tube or an antegrade stent.

Treatment is often based on opinion or local resources, leading to widespread variation in practice across the UK.

Clinical question: What is the best way to manage cancer related ureteric obstruction in patients with bladder cancer?

Clinical evidence (see also full evidence review)

The evidence is summarised in tables 146 to 151

Evidence statements

Very low quality evidence was identified from 30 retrospective observational studies. All studies report an improvement of renal function and symptom relief in a majority of patients after percutaneous nephrostomy (PCN) or stent placement. Seven studies reported the comparative outcomes of patients who received PCN and those who received retrograde stents for malignant obstructions. Ku *et al.* (2004) reported that both ureteral stenting and PCN resulted in a decrease of serum creatinine, with no significant difference between groups. One study reported that serum creatinine increased in all patients (n=110), with a smaller elevation of creatinine levels in the PCN group than in the stent group (Chang *et al.*

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2012). This study also reported that residual hydronephrosis after diversion was more common in the stent group than the PCN group (65% versus 27%).

Four studies reported complications of PCN (n=218) and ureteral stents (n=156). Similar rates of complications were reported with ureteral stents (28.8%) and PCN (30.3%). A further study (Chang *et al.* 2012) reported that the stent group had more frequent UTI, including urosepsis and pyelonphritis, than the PCN group, although this difference was non-significant.

Two studies reported overall survival in patients who underwent stenting and in those who underwent PCN (Kanou *et al.*, 2007; Wong *et al.*, 2007). Average overall survival was 5.6 and 9.2 months for ureteral stents and 5.9 and 6.5 months for PCN.

One study reported that 21% (11/52) of patients were treated with chemotherapy after successful drainage of the kidneys. It is not reported which intervention these patients received (Hubner *et al.* 1993). In one study, 1/30 patients with bladder cancer had a total cystectomy with urinary diversion for muscle-invasive disease after relief of obstruction (Chitale *et al.*, 2002).

One study reported that responses to quality of life surveys were not significantly different for patients receiving nephrostomy tubes (n=16), double-J stents (n=15) or nephroureteral stents (NUS, n=15). Patients who had double-J stents reported more pain, dysuria, and urinary frequency, compared with nephrostomy tubes and NUS at 30 and 90 days after placement (Monsky *et al.*, 2013).

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Table 146: GRADE evidence profile: What is the best way to manage cancer related ureteric obstruction in patients with bladder cancer? Open nephrostomy, percutaneous nephrostomy, retrograde stents

Quality assessment							No of patients			Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Open nephrostomy**	**PCN**	**Retrograde stents**	**Relative (95% CI)**	**Absolute**	**Quality**
Improvement of renal function (assessed with: proportion with normal renal function 2 weeks after procedure)												
1[1]	observational study[2]	none	none	serious[3]	serious[4]	none	60/88 (68%) not reported separately by procedure			-	-	VERY LOW
Improvement of renal function (assessed with: proportion with improved renal function 2 weeks after procedure)												
1[1]	observational study[2]	none	none	serious[3]	serious[4]	none	21/88 (24%) not reported separately by procedure			-	-	VERY LOW
Symptom relief												
0	No evidence available											
Treatment-related morbidity												
1[1]	observational study[2]	none	none	serious[3]	serious[4]	none	8/14 (57%)	13/53 (24%)	5/27 (19%)	-	-	VERY LOW
Overall survival												
1[1]	observational study[2]	none	none	serious[3]	serious[4]	none	3.8 months	6.5 months		-	-	VERY LOW
Subsequent chemotherapy												
0	No evidence available											
Subsequent cystectomy												
0	No evidence available											
Health-related quality of life												
0	No evidence available											

[1] Zadra et al. 1987 [2] case series [3] Included patients with primary tumour sites other than the bladder [4] Small sample size limits precision of the outcome

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Table 147: GRADE evidence profile: What is the best way to manage cancer related ureteric obstruction in patients with bladder cancer? Retrograde stents for malignant obstructions

Quality assessment							No of patients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Retrograde stents	Effect	Quality
Improvement of renal function (measured with: Change in serum creatinine level pre- and post-procedure (mg/dL)									
3[1]	observational studies[2]	serious[3]	none	serious[4]	none	none	N=313	Scr decreased in all studies by 34% to 57%	VERY LOW
Symptom relief (follow-up mean 11 months; assessed with: Success of retrograde stent - resolution of hydronephrosis and flank pain, or renal failure)									
1[5]	observational studies[2]	None	none	serious[4]	serious[6]	none	50/90 (55.6%)	-	VERY LOW
Treatment-related morbidity (assessed with: Overall complication rate e.g. catheter blockage, hematuria, UTI)									
3[1]	observational studies[2]	serious[3]	none	serious[4]	none	none	198/302 (65.6%)	-	VERY LOW
Overall survival									
4[7]	observational studies[2]	serious[3]	none	serious[4]	None	none	374	Average overall survival range 2.2 to 11.1 months	VERY LOW
Subsequent chemotherapy									
1[8]	observational studies[2]	none	none	serious[4]	serious[6]	none	26/61 (42.6%)	-	VERY LOW
Subsequent cystectomy									
0	No evidence available								
Health-related quality of life									
0	No evidence available								

[1] Shekarriz et al. 1999; Ganatra & Loughlin 2005; Kamiyama et al. 2011 [2] case series [3] In Shekarriz et al. (1999) patients received either stent or nephrostomy, which were not reported separately [4] Studies include patients with primary tumour sites other than the bladder [5] Chung et al. 2004 [6] Small sample size limits precision [7] Shekarriz et al. 1999; Ganatra & Loughlin 2005; Kamiyama et al. 2011; Izumi et al. 2011 [8] Izumi et al. 2011

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Table 148: GRADE evidence profile: What is the best way to manage cancer related ureteric obstruction in patients with bladder cancer? Percutaneous nephrostomy for malignant obstructions secondary to bladder cancer

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Percutaneous nephrostomy		
Improvement in renal function (assessed with: Proportion improved to normal renal function)									
1[1]	observational studies[2]	none	none	none	serious[3]	None	19/23 (82.6%)	-	VERY LOW
Symptom relief									
0	No evidence available								
Treatment-related morbidity (assessed with: Overall complication rate e.g. slippage of PCN tube, hematuria)									
3[4]	observational studies[2]	none	none	none	serious[3]	None	22/109 (20.2%)	-	VERY LOW
Overall survival (follow-up mean 16-34 months, range)									
3[4]	observational studies[2]	none	none	none	serious[3]	None	37/97 (38.1%)[5]	-	VERY LOW
Subsequent chemotherapy									
1[1]	observational studies[2]	none	none	none	serious[3]	None	11/23 (47.8%)	-	VERY LOW
Subsequent cystectomy									
3[4]	observational studies[2]	none	none	none	serious[3]	None	66/142 (46.5%)[6]	-	VERY LOW
Health-related quality of life									
0	No evidence available								

[1] Ekici et al. 2001 [2] case series [3] Small sample size limits precision [4] Ekici et al. 2003; Gupta et al. 2007; El-Tabey et al. 2005 [5] Median overall survival was 4.9 months (range 1-14) in Ekici et al. 2001 [6] In El-Tabey et al. 2005, 23/61 patients had inoperable locally advanced disease. 10/61 had palliative cystectomy without lymphadenectomy. 26/61 had radical cystectomy with intent to cure.

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Table 149: GRADE evidence profile: What is the best way to manage cancer related ureteric obstruction in patients with bladder cancer? Percutaneous nephrostomy for malignant obstructions

Quality assessment							No of patients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCN	Effect	Quality
Improvement in renal function (assessed with: Serum creatinine levels, Better indicated by lower values)									
6[1]	observational studies[2]	serious[3]	none	serious[4]	none	none	N=795	All studies reported a decrease in Scr after procedure	VERY LOW
Improvement in renal function (improved to normal function or significant improvement in function)									
2[5]	observational studies[2]	serious[3]	none	serious[4]	none	none	208/241 (86.3%)	-	VERY LOW
Symptom relief (assessed with: Relief of obstruction)									
2[6]	observational studies[2]	serious[3]	none	serious[4]	none	none	151/248 (60.9%)	-	VERY LOW
Treatment-related morbidity (assessed with: Complication rate - per person or per ureter)									
11[7]	observational studies[2]	serious[3]	none	serious[4]	none	none	447/1523 (29.3%)	-	VERY LOW
Overall survival									
11[8]	observational studies[2]	none	none	serious[4]	none	none	N=1299	Average OS ranged from 3.2 to 12.2 months	VERY LOW
Subsequent chemotherapy and/or radiotherapy									
1[9]	observational studies[2]	none	none	serious[4]	serious[10]	none	27/38 (71.1%)	-	VERY LOW
Subsequent cystectomy (assessed with: patients with bladder cancer undergoing surgery after nephrostomy)									
1[11]	observational studies[2]	none	none	serious[4]	serious[10]	none	4/29 (13.8%)	-	VERY LOW
Health-related quality of life (measured with: EORTC-QLQ; Better indicated by lower values)									
1[12]	observational studies[2]	none	none	serious[4]	none	none	270	No improvement in QoL	VERY LOW

[1] Meyer et al. 1980; Ishioka et al. 2008; Vehmas et al. 1988; Lau et al. 1995; Aravantinos et al. 2007; Liatsikos et al. 2009; [2] case series; [3] Patients with malignant and benign obstructions not reported separately in Vehmas et al. (1988) and Pappas et al (2000) and complication rate not reported separately in Lau et al. (1995); [4] Studies include patients with primary tumour sites other than the bladder; [5] Meyer et al. 1980; Pappas et al. 2000; [6] Vehmas et al. 1988; Liatsikos et al. 2009; [7] Meyer et al. 1980; Ishioka et al. 2008; Lienert et al. 2009; Vehmas et al. 1988; Lau et al. 1995; Aravantinos et al. 2007; Fallon et al. 1980; Carrafiello et al. 2006; Liatsikos et al. 2009; Kinn & Ohlsen 2003; Pappas et al. 2000 [8] Radecka et al. 2006; Lau et al. 1995; Aravantinos et al. 2007; Fallon et al. 1980; Meyer et al. 1980; Ishioka et al. 2008; Watkinson et al. 1993; Sheikh et al. 2007; Lienert et al. 2009; Kinn & Ohlsen 2003; Pappas et al. 2000; [9] Meyer et al. 1980; [10] Small sample size limits precision; [11] Fallon et al. 1980; [12] Aravantinos et al. 2007

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Table 150: GRADE evidence profile: What is the best way to manage cancer related ureteric obstruction in patients with bladder cancer? Retrograde stent versus percutaneous nephrostomy for malignant obstructions

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Urinary stent	Percutaneous nephrostomy	Relative (95% CI)	Absolute	Quality
Improvement of renal function (assessed with: Pre-procedure and post-procedure serum creatinine levels)											
3[1]	observational studies[9]	serious[2]	none	serious[3]	serious[5]	none	N=185	N=148	-		VERY LOW
Symptom relief (assessed with: Residual hydronephrosis)											
1[4]	observational studies[9]	serious[2]	none	serious[3]	serious[5]	none	43/66 (65.2%)	12/44 (27.3%)	RR 2.39 (1.43 to 3.99)	379 more per 1000 (from 117 more to 815 more)	VERY LOW
Treatment-related morbidity (assessed with: Overall complication rate)											
4[6]	observational studies[9]	none	none	serious[3]	serious[5]	none	45/156 (28.8%)	66/218 (30.3%)	-		VERY LOW
Overall survival											
2[7]	observational studies[9]	none	none	serious[3]	serious[5]	none	N=106 Average OS = 5.6 and 9.2 mo	N=71 Average OS = 5.9 and 6.5 mo	-		VERY LOW
Subsequent chemotherapy											
1[8]	observational studies[9]	none	none	serious[3]	serious[5]	none	11/52 (21.2%)		-		VERY LOW
Subsequent cystectomy (follow-up 10-34 months)											
1[10]	observational studies[9]	none	none	serious[3]	serious[5]	none	1/30 (3.3%)[11]		-		VERY LOW
Health-related quality of life											
1[12]	observational studies	none	none	none	serious[5]	none	N=15	N=16	No differences in QoL at 7, 30 or 90 days.		VERY LOW

[1] Ku et al. 2004; Kanou et al. 2007; Chang et al. 2012; [2] Malignant and benign obstructions not reported separately in Chang et al. 2012; [3] Studies include patients with primary tumour sites other than the bladder; [4] Chang et al. 2012; [5] Small sample size / low number of events limits precision; [6] Ku et al. 2004; Kanou et al. 2007; Wong et al. 2007; Hubner et al. 1993; [7] Kanou et al. 2007; Wong et al. 2007; [8] Hubner et al. 1993; [9] Case series; [10] Chitale et al. 2002; [11] One patient out of 30 with bladder cancer had a total cystectomy with urinary diversion for muscle-invasive disease after relief of obstruction in Chitale et al. (2002); [12] Monsky et al. 2013

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Table 151: GRADE evidence profile: What is the best way to manage cancer related ureteric obstruction in patients with bladder cancer? Subcutaneous nephro-vesical/ nephro-cutaneous bypass for malignant obstructions

Quality assessment							No of patients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subcutaneous nephro-vesical/ nephro-cutaneous bypass	Effect	Quality
Improvement of renal function (follow-up mean 12.9 months; Better indicated by lower values)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	N=524	-	VERY LOW
Symptom relief (follow-up mean 12.9 months; assessed with: Complete reduction of hydronephrosis)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	42/52 (80.8%)	-	VERY LOW
Treatment-related morbidity (follow-up mean 12.9 months; assessed with: UTI)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	15/52 (28.8%)	-	VERY LOW
Overall survival (follow-up mean 12.9 months)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	4/52 (7.7%)	-	VERY LOW
Subsequent chemotherapy									
0	No evidence available								
Subsequent cystectomy									
0	No evidence available								
Health-related quality of life (follow-up mean 12.9 months; measured with: 0=very poor, 10=excellent; range of scores: 0-10; Better indicated by higher values)									
1[1]	observational studies[2]	none	none	none	serious[3]	none	N=525	-	VERY LOW

[1] Schmidbauer et al. 2009 (abstract only); [2] Case series; [3] Small sample size limits the precision of this outcome; [4] Mean serum creatinine decreased from mean of 6.1 (range 2.3-12.8) to 1.55 (range 0.55-6.3) mg/%; [5] Mean quality of life score was 3.6 (range 0-6) pre-operatively, and 7.8 (range 5-9) post-operatively

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Discuss treatment options with people who have locally advanced or metastatic bladder cancer with ureteric obstruction. Include in your discussion:** • **prognosis of their cancer and** • **advantages and disadvantages of the treatment options, including best supportive care.** **Consider percutaneous nephrostomy or retrograde stenting (if technically feasible) for people with locally advanced or metastatic bladder cancer and ureteric obstruction who need treatment to relieve pain, treat acute kidney injury or improve renal function before further treatment.** **If facilities for percutaneous nephrostomy or retrograde stenting are not available at the local hospital, or if these procedures are unsuccessful, discuss the options with a specialist urology multidisciplinary team for people with bladder cancer and ureteric obstruction.**
Relative value placed on the outcomes considered	The GDG considered all outcomes except subsequent cystectomy rate to be important as survival and quality of life have the greatest impact on the patient. Subsequent cystectomy was not considered to be useful because it doesn't impact on treatment choice. Success of stent/PCN was not stated as an outcome in the PICO but was considered by the GDG when making recommendations. It was considered important because failure of access is detrimental for the patient.
Quality of the evidence	The quality of the evidence was very low as assessed with GRADE. The evidence was limited by a lack of high quality studies. The included studies had heterogeneous patient groups and were not specific to patients with bladder cancer related urinary obstruction. The lack of high quality evidence made it difficult for the GDG to give definitive guidance and decide which treatment was most beneficial. The GDG considered that evidence around patient-reported outcomes was lacking. The recommendation to discuss treatment options and prognosis with the patient was made based on clinical experience, with the aim of improving patient information to support patient choice. Referral to a specialist team was also based on the clinical experience of the GDG to improve the standard of clinical management and to improve equity of access to clinical care.
Trade-off between clinical benefits and harms	The benefits of the recommendations made include potential for improvement in patient information and counselling, improved patient choice, and reduced discussion between the urologist and radiologist. These recommendations provide guidance and therefore treatment should not based on the personal preference of the clinician. Improved

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	equality of access to treatment is also a potential benefit of the recommendations. The GDG identified no harms from the recommendations made.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed. The potential costs include increased use of interventions in appropriate cases and increased discussion with specialist teams, which may incur small costs. This was balanced against the savings from the avoidance of inappropriate interventions.
Other considerations	No equalities issues were identified. The GDG considered that current practice is highly variable. These recommendations may increase involvement of specialist teams in some areas. There is the potential for change in the use of stenting and PCN depending on current practice, especially where there is an extreme use of one intervention over the other. The GDG patient representatives highlighted the importance of patient choice and involvement in decision making. Informed patient choice was considered a priority for this area.

6.2.3 Intractable haematuria

Intractable bleeding from the bladder is one of the most serious terminal complications for patients with bladder cancer because it is usually painful because clots form and block bladder drainage, it is frightening for the affected person and their carers, it is difficult to manage, and almost certainly means that the person will have to be admitted to hospital for care. Intractable bladder bleeding may occur before the person is in a terminal phase but it may be the terminal event for people with bladder cancer. This means that they may die in hospital and certainly may lose precious hours and days that they would have rather spent at home with their family.

Severe bleeding can arise from the bladder cancer itself, or from the effects of radiation or cyclophosphamide, and infection can complicate and worsen bleeding from all of these. Patients with severe haematuria are often elderly and already extremely frail.

Treatments for intractable bleeding include:

- Palliative TURBT
- Tranexamic acid
- Palliative radiotherapy
- Embolisation
- Palliative chemotherapy
- Urinary diversion

Clinical question: What specific interventions are most effective for patients with incurable bladder cancer and intractable bleeding?

Clinical evidence (see also full evidence review)

The evidence is summarised in tables 152 to 154. No evidence was identified for palliative TURBT, urinary diversion, or tranexamic acid.

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Evidence statements

Palliative radiotherapy

One observational study (Srinivasan *et al.*, 1994) provided very low quality evidence about the relative effectiveness of hypofractionated (two-fraction) radiotherapy and conventional palliative radiotherapy in 41 patients selected by performance status. 59% of those receiving two-fraction radiotherapy had clearance of haematuria compared to 16% of those receiving conventional palliation (RR 3.74, 95% CI 1.25 to 11.19). One observational study of 32 patients also selected for hypofractionated radiotherapy if they had a poor performance status (Lacarriere *et al.*, 2013). After 2 weeks of radiotherapy, 79% of patients receiving hypofractionated radiotherapy (20Gy/5 fractions/1 week) and 54% of the conventional radiotherapy (30Gy/10 fractions/2 weeks) group had complete clearance of hematuria (RR 1.47, 95% CI 0.84 to 2.55). At six months 37% and 23% in the hypofractionated and conventional radiotherapy group had no haematuria (RR 1.60, 95% CI 0.5 to 5.06).

Embolisation

Four observational studies including a total of 67 patients provided very low quality evidence for embolisation of the internal iliac arteries. Immediate control of bleeding was seen in 57/67 (85%) patients, with control rates ranging from 82% to 100% across studies. Permanent control of bleeding with mean follow-up ranging from 10 to 22 months across studies was achieved in 34/66 (51.5%) patients. The range of permanent bleeding control rates ranged from 43% to 100% across studies. After embolisation, 27% of patients required transfusion for haematuria. None of the studies reported any major treatment-related complications, except for Jenkins & McIvor (1996), where one patient who did not receive prophylactic antibiotics died from septic shock 12 hours after embolisation. Ligouri *et al.* (2010) reported that minor complications were post-embolisation syndrome (27%), fever (11%), gluteal pain (14%), and nausea (2%).

Chemotherapy

One observational study (Mantadakis *et al.*, 2003) provided very low quality evidence of regional intra-arterial chemotherapy (RIAC) for the symptomatic relief of patients with advanced bladder cancer who were unsuitable for surgery. Gross haematuria was present in all 32 patients prior to RIAC, which had resolved in 24/32 (75%) after treatment. There were no hemorrhagic, thrombotic or embolic complications, and no episodes of nausea or emesis. One patient developed grade three mucositis.

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Table 152: GRADE evidence profile: The effectiveness of hypofractionated radiotherapy versus conventional palliative radiotherapy for intractable bleeding

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hypofractionated RT**	**Conventional RT**	**Relative (95% CI)**	**Absolute**	**Quality**
Clearance of haematuria											
1[1]	observational studies	none	none	none	serious[2]	none	13/22 (59.1%)	3/19 (15.8%)	RR 3.74 (1.25 to 11.19)	433 more per 1000 (from 39 more to 1000 more)	VERY LOW
Clearance or improvement of haematuria (assessed with: Stopped completely or haematuria but without hospitalisation)											
1[1]	observational studies	none	none	none	serious[2]	none	19/22 (86.4%)	13/19 (68.4%)	RR 1.26 (0.89 to 1.79)	178 more per 1000 (from 75 fewer to 541 more)	VERY LOW
Clearance of haematuria at 2 weeks (Common Terminology Criteria for Adverse Events)											
1[3]	observational studies	none	none	none	serious[2]	none	15/19 (78.9%)	7/13 (53.8%)	RR 1.47 (0.84 to 2.55)	253 more per 1000 (from 86 fewer to 835 more)	VERY LOW
Clearance of haematuria at 6 months (Common Terminology Criteria for Adverse Events)											
1[3]	observational studies	none	none	none	serious[2]	none	7/19 (36.8%)	3/13 (23.1%)	RR 1.60 (0.5 to 5.06)	138 more per 1000 (from 115 fewer to 937 more)	VERY LOW
Requirement for transfusion											

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Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypofractionated RT	Conventional RT	Relative (95% CI)	Absolute	
0	No evidence available										
Patient-reported distress											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity											
0	No evidence available										
Quality of life											
0	No evidence available										

[1] Srinivasan et al. (1994); [2] Low number of events/small sample size limits precision; [3] Lacarriere et al. (2013)

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Table 153: GRADE evidence profile: The effectiveness of embolisation for intractable bleeding

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Embolisation	Control	Relative (95% CI)	Absolute	Quality
Initial control of bleeding											
4[1]	observational studies	none	none	none	serious[2]	none	57/67 (85.1%)	n/a	-	-	VERY LOW
Permanent control of bleeding (mean follow-up ranged from 10-22 months across studies)											
4[1]	observational studies	none	none	none	serious[2]	none	34/66 (51.5%)	n/a	-	-	VERY LOW
Requirement for transfusion (after treatment)											
4[1]	observational studies	none	none	none	serious[2]	none	18/67 (26.9%)	n/a	-	-	VERY LOW
Patient-reported distress											
0	No evidence available										
Treatment-related mortality											
4[1]	observational studies	none	none	none	serious[2]	none	1/67 (1.5%)[3]	n/a	-	-	VERY LOW
Treatment-related morbidity											
4[1]	observational studies	none	none	none	serious[2]	none	N=67[4]	n/a	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Ligouri et al. 2010; El-Assmy & Mohsen 2007; Nabi et al. 2003; Jenkins & McIvor 1996; [2] Small sample size / low number of events limits precision; [3] One patient who did not receive prophylactic antibiotics died from septic shock 12 hours after embolisation (Jenkins & McIvor 1996); [4] All studies reported no major complications. Ligouri et al. (2010) reported minor complications: post-embolisation syndrome 27%, fever 11%, gluteal pain 14%, nausea 2%. Jenkins & McIvor (1996) reported that 3/10 patients developed moderate buttock and thigh pain lasting a maximum of 3 days.

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Table 154: GRADE evidence profile: The effectiveness of regional intra-arterial chemotherapy (RIAC) for intractable bleeding

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RIAC**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Successful treatment of bleeding (resolution of gross haematuria)											
1[1]	observational studies	none	none	none	serious[2]	none	24/32 (75%)	n/a	-	-	VERY LOW
Requirement for transfusion											
0	No evidence available										
Patient-reported distress											
0	No evidence available										
Treatment-related mortality											
0	No evidence available										
Treatment-related morbidity (assessed with: hemorrhagic, thrombotic or embolic complications)											
1[1]	observational studies	none	none	none	serious[2]	none	0/32 (0%)	n/a	-	-	VERY LOW
Grade 3-4 adverse events											
1[1]	observational studies	none	none	none	serious[2]	none	1/32 (3.1%)	n/a	-	-	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] Mantadakis et al. 2004; [2] Small sample size / low number of events limits precision

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Evaluate the cause of intractable bleeding with the local urology team.** **Consider hypofractionated radiotherapy or embolisation for people with intractable bleeding caused by incurable bladder cancer.** **If a person has intractable bleeding caused by bladder cancer and radiotherapy or embolisation are not suitable treatments, discuss further management with a specialist urology multidisciplinary team.**
Relative value placed on the outcomes considered	The GDG considered successful treatment of bleeding and treatment-related morbidity to be the most important outcomes because they are distressing events for patients. Requirement for transfusion was not considered a useful outcome because it is a surrogate outcome. Stopping bleeding was considered more important than transfusion. Treatment-related mortality wasn't considered useful because the risk of death from the interventions is very low. Patient-reported distress and health-related quality of life were specified as outcomes in the PICO but were not reported in the evidence.
Quality of the evidence	The quality of the evidence was very low as assessed by GRADE. The main limitation of the evidence was the lack of randomised trials comparing interventions for intractable bleeding. The included studies were limited by small sample sizes and poorly defined patient groups. These issues meant that the GDG were unable to effectively compare different treatment approaches and were restricted to making more general recommendations. The recommendation to involve the urological team in the evaluation of bleeding was based on GDG clinical experience. The GDG have also assumed that the current NICE guidance on supportive and palliative care would support the recommendation of referral to specialist palliative care teams.
Trade-off between clinical benefits and harms	The GDG considered the potential benefits of the recommendations to include improved access to appropriate management, particularly referral to palliative specialists. Improved symptom control and better end-of-life care. Reduced time spent in hospital and a better experience for carers. The GDG considered that potential harms were likely to be small but may include some morbidity from embolisation and radiotherapy. The GDG considered that the substantial benefits were likely to

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	outweigh the relatively small risk of potential harms.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GDG considered that the recommendations were likely to lead to increased embolisation and radiotherapy costs, increased palliative care costs, and increased time from urological teams. The GDG balanced this against the potential savings from reduced time in hospital, reduced need for acute services, and a reduction in transfusion rates. The GDG thought that there is likely to be a net saving to the NHS.
Other considerations	The recommendation aims to promote access and reduce geographical inequities. The GDG were unsure as to the full extent of the change in practice required to implement the recommendations. However, they expected there to be a modest increase in the use of radiotherapy and embolisation. The GDG also noted that the recommendations may increase awareness of end-of-life issues for urology patients and increase involvement for urology teams. The practicalities of how best to arrange palliative care/urology consultations for patients in the community, particularly in care homes, were also considered.

6.2.4 Intractable pelvic pain

Intractable pelvic pain is one of the most serious end of life complications for people with bladder cancer.The pain is very distressing for them and their family/carers and is difficult to manage. It is important to take into account prognosis in shared decision making about intractable pelvic pain. It is not only the treatment but also where this takes place (for example home, hospital, hospice) that is important to the person and their family/carers. The effects of poor management of intractable pelvic pain can also markedly worsen the bereavement process for family and carers.

Important issues regarding pelvic pain in people with incurable bladder cancer include:

- Communication with the person and their family and explanation that this could be a terminal event
- The treatment options for the pain
- Other supportive care options
- Options for place of care: hospital, hospice, home, nursing home

Clinical question: What specific interventions are most effective for patients with incurable bladder cancer and pelvic pain?

Clinical evidence (see also full evidence review)

The evidence is summarised in tables 155 to 157.

Evidence statements

Radiotherapy

One observational study (Srinivasan *et al.*, 1994) provided very low quality evidence about the relative effectiveness of hypofractionated (two-fraction) radiotherapy and conventional palliative radiotherapy in 41 patients selected by performance status. Pain improved in 73% of those treated with two-fraction radiotherapy compared to 37% of those treated with

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conventional palliation (RR 1.97, 95% CI 1.04 to 3.75). One study (58 patients) of hypofractionated radiotherapy and one study (12 patients) of short course accelerated 3D-CRT both reported a decrease in patient-reported pain after treatment, as measured on a visual analogue scale (VAS). These two studies reported an acute Grade 1-2 GI toxicity rate of 21% and an acute Grade 1-2 GU toxicity rate of 35% (Kouloulias *et al.*, 2013; Caravatta *et al.*, 2012). One study provided very low quality evidence for quality of life in 13 patients, reporting no statistically significant difference between baseline and post-treatment scores, although an improvement was noted in all indexes (Caravatta *et al.*, 2012).

Chemotherapy

Very low quality evidence from one prospective nonrandomised phase II study (30 patients) of second-line gemcitabine chemotherapy in cisplatin-refractory patients, reported that VAS pain values significantly improved in the group of patients who responded to chemotherapy (Albers *et al.*, 2002). One retrospective study of 35 patients receiving second-line gemcitabine and paclitaxel chemotherapy, reported very low quality evidence that 80% (28/35) of patients reported a decrease in VAS scores without increasing the dose of analgesics or had a decrease in analgesic consumption (Miyata *et al.*, 2012). The most common toxicity reported in both studies was Grade 3-4 leucopenia (36% with gemcitabine monotherapy, 14% with gemcitabine/paclitaxel). Very low quality evidence for quality of life as measured by the 10-point Spitzer scale was reported in one study (Albers *et al.*, 2002). Mean quality of life scores for patients who did not respond to chemotherapy decreased before and after treatment (7.8 ±2.4 to 6.7 ±2.2), representing a worsening of quality of life. Quality of life scores for responders were similar before and after treatment (8.0 ±1.6 to 8.1 ±2.5).

Nerve block

Evidence of very low quality was provided by five studies reporting on the treatment of pelvic pain with a hypogastric plexus block. Two studies reported that satisfactory pain relief was achieved in 72% (133/185) of patients after one or two procedures, who all reported a VAS pain score of 8 or more out of 10 (worst possible pain) before the procedure (De Leon-Casasola *et al.*, 1993; Plancarte *et al.*, 1997). One study of 28 patients reported a mean pain reduction of 70% as assessed with verbal and visual analogue scales before and after treatment, although mean patient scores at baseline and follow-up were not reported (Plancarte *et al.*, 1990). One study reported that VAS pain scores decreased from baseline at 24h, 1 week, 1 month and 2 months after treatment ($p<0.05$), but at three months mean scores increased and were no different from baseline (Gamal *et al.*, 2006). Four studies (including 225 patients) provided very low quality evidence for treatment-related morbidity, with three studies reporting no intraoperative complications and one study (Gamal *et al.*, 2006) reporting intravascular puncture (n=2, 13%) and urinary injury (n=4, 27%).

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Table 155: GRADE evidence profile: The effectiveness of radiotherapy for cancer-related pelvic pain in patients with advanced cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypofractionated RT	Conventional RT	Relative (95% CI)	Absolute	Quality
Relief or improvement in pain (assessed with: Opiates discontinued or at least a 50% reduction in opiate requirement)											
1[1]	observational studies	serious[2]	none	none	serious[3]	none	16/22 (72.7%)	7/19 (36.8%)	RR 1.97 (1.04 to 3.75)	357 more per 1000 (from 15 more to 1000 more)	VERY LOW
Patient-reported pain (assessed with: Mean (SD) Visual Analog Scale (VAS) score – scale 0 (no pain) to 10 (most pain))											
1[4]	observational studies	none	none	none	serious[3]	none	N=58	n/a	-	4.2 ±1.1 before RT and 1.8 ±0.6 after RT (no p value)	VERY LOW
Patient-reported pain (assessed with: Mean (SD) Visual Analog Scale (VAS) score – scale 0 (no pain) to 10 (most pain))											
1[5]	observational studies	none	none	none	serious[3]	none	N=12	n/a	-	6 ±2 before RT and 3 ±2.3 after RT (p=.0002)	VERY LOW
Treatment-related morbidity (assessed with: acute Grade 1-2 GI toxicity; follow-up 3-6 months)											
2[4,5]	observational studies	none	none	none	serious[3]	none	18/85 (21.2%)	n/a	-	-	VERY LOW
Treatment-related morbidity (assessed with: acute Grade 1-2 GU toxicity; follow-up 3-6 months)											
2[4,5]	observational studies	none	none	none	serious[3]	none	30/85 (35.3%)	n/a	-	-	VERY LOW
Health-related quality of life (assessed with: Cancer Linear Analog Scale, measured well-being, fatigue, and ability to perform daily activities)											
1[5]	observational studies	serious[6]	none	none	serious[3]	none	N=13	n/a		No significant difference from baseline to post-treatment	VERY LOW

[1] Srinivasan et al. (1994); [2] Patients selected for treatments based on performance status. Hypofractionated group were older and with poor performance status (WHO grade 4 or more). No pain data for 7 patients; [3] Low number of events/small sample size limits precision; [4] Kouloulias et al. (2013); [5] Caravatta et al. (2012) short course accelerated 3D-CRT; [6] Unclear if patients completing the QoL measure had received RT for pain management.

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Table 156: GRADE evidence profile: The effectiveness of chemotherapy for cancer-related pelvic pain in patients with advanced cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy	Control	Relative (95% CI)	Absolute	Quality
Patient-reported pain (non-responders to chemotherapy) (follow-up mean 8.4 months; measured with: Visual Analog Scale (7-point scale); Better indicated by higher values)											
1[1]	observational studies	none	none	none	serious[2]	none	15	-	-	5.3±1.8 before and 4.8±1.5 after CT (increase in pain, no p value)	VERY LOW
Patient-reported pain (responders to chemotherapy) (follow-up mean 8.4 months; measured with: Visual Analog Scale (7-point scale); Better indicated by higher values)											
1[1]	observational studies	None	none	none	serious[2]	none	13	-	-	4.3±1.9 before and 5.8 ±1.3 after CT (decrease in pain, p<0.05)	VERY LOW
Patient-reported pain (follow-up median 10 months; assessed with: Improved pain score on VAS)											
1[3]	observational studies	none	none	none	serious[2]	none	24/35 (68.6%)	-	-	-	VERY LOW
Decrease in analgesic consumption (follow-up median 10 months)											
1[3]	observational studies	none	none	none	serious[2]	none	12/35 (34.3%)	-	-	-	VERY LOW
Decrease in analgesic consumption or decrease in VAS score without increasing analgesic dose (follow-up median 10 months)											
1[3]	observational studies	none	none	none	serious[2]	none	28/35 (80%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia (Gem)											
1[1]	observational studies	none	none	none	serious[2]	none	10/28 (35.7%)	-	-	-	VERY LOW
Grade 3-4 Leucopenia (Gem/Pac)											

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Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chemotherapy**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
1[3]	observational studies	none	none	none	serious[2]	none	5/35 (14.3%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (Gem)											
1[1]	observational studies	none	none	none	serious[2]	none	3/28 (10.7%)	-	-	-	VERY LOW
Grade 3-4 Thrombocytopenia (Gem/Pac)											
1[3]	observational studies	none	none	none	serious[2]	none	2/35 (5.7%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (Gem)											
1[1]	observational studies	none	none	none	serious[2]	none	3/28 (10.7%)	-	-	-	VERY LOW
Grade 3-4 Anaemia (Gem/Pac)											
1[2]	observational studies	none	none	none	serious[2]	none	2/35 (5.7%)	-	-	-	VERY LOW
Health-related quality of life (Responders to chemotherapy) (measured with: Spitzer index 10-point scale; Better indicated by higher values)											
1[1]	observational studies	none	none	none	serious[2]	none	13	-	-	8.0 ±1.6 before and 8.1 ±2.5 after CT (no p value)	VERY LOW
Health-related quality of life (Non-responders to chemotherapy) (measured with: Spitzer index 10-point scale; Better indicated by higher values)											
1[1]	observational studies	none	none	none	serious[2]	none	15	-	-	7.8 ±2.4 before and 6.7 ±2.2 after CT (no p value)	VERY LOW

[1] Albers et al. 2002 (2nd line Gemcitabine); [2] Small sample size / low number of events limits precision; [3] Miyata et al. 2012 (2nd line Gemcitabine/Paclitaxel)

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Table 157: GRADE evidence profile: The effectiveness of hypogastric plexus block for cancer-related pelvic pain in patients with advanced cancer

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypogastric plexus block	Control	Relative (95% CI)	Absolute	Quality
Patient-reported pain (assessed with: Satisfactory pain relief after 1 or 2 procedures (all patients VAS score >8/10 (worst possible pain) before treatment)											
2[1]	observational studies	serious[2]	none	serious[3]	serious[4]	none	133/185 (71.9%)	n/a	-	-	VERY LOW
Patient-reported pain (assessed with: Visual and verbal analogue scale)											
1[5]	observational studies	serious[6]	none	serious[3]	serious[4]	none	N=28	n/a	-	mean reduction in pain =70%	VERY LOW
Patient-reported pain (assessed with: VAS score (scale 0 (no pain) to 10 (worst pain))											
1[7]	observational studies	serious[6]	none	serious[3]	serious[4]	none	N=30	n/a	-	see footnote8	VERY LOW
Patient-reported pain (assessed with: moderate or complete pain relief (4-grade subjective analogue scale - none, mild, moderate, complete))											
1[9]	observational studies	none	none	serious[10]	serious[4]	none	6/10 (60%)	n/a	-	-	VERY LOW
Treatment-related morbidity											
4[1,7,9]	observational studies	none	none	serious[3]	serious[4]	none	6/225 (2.7%)	n/a	-	see footnote[11]	VERY LOW
Health-related quality of life											
0	No evidence available										

[1] De Leon-Casasola et al.1993; Plancarte et al. 1997; [2] In Plancarte et al. (1997) only patients who had a positive response to diagnostic block received the neurolytic block; [3] Studies include mostly women with gynaecological cancers; [4] Low number of events / small sample size limits precision; [5] Plancarte et al. 1990; [6] Poorly reported outcomes and method of outcome assessment. Mean scores not provided. [7] Gamal et al. 2006; [8] Scores decreased from baseline at 24h, 1 week, 1 month and 2 months after block (p<0.05). At 3 months there was no difference from baseline; [9] Cariati et al. 2002; [10] Mostly colorectal and uterine cancer patients; [11] All studies except for Gamal et al. 2006 reported no intraoperative or long-term complications. Gamal et al. (2006) reported Intravascular puncture (n=2, 13%), urinary injury (n=4, 27%)

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Evaluate the cause of pelvic pain with the local urology team.** **Consider, in addition to best supportive care, 1 or more of the following to treat pelvic pain caused by incurable bladder cancer:** • **hypofractionated radiotherapy if the person has not had pelvic radiotherapy** • **nerve block** • **palliative chemotherapy.**
Relative value placed on the outcomes considered	The GDG considered successful patient-reported pain to be the most important outcome because pain can be distressing to patients. Health-related quality of life was also considered to be an important outcome for both patients and carers. All of the outcomes specified in the PICO were reported in the evidence and no additional outcomes (i.e. not specified in the PICO) were used to make recommendations.
Quality of the evidence	The quality of the evidence was very low as assessed by GRADE. The main limitation of the evidence was the lack of randomised trials comparing interventions for pelvic pain. The included studies were limited by small sample sizes and poorly defined patient groups. In addition, some studies included people that did not have bladder cancer. These issues meant that the GDG were unable to effectively compare different treatment approaches and were restricted to making more general recommendations. The recommendation to involve the urological team in the evaluation of pain was based on GDG clinical experience. The GDG have also assumed that the current NICE guidance on supportive and palliative care would support the recommendation of referral to specialist palliative care teams.
Trade-off between clinical benefits and harms	The GDG considered the potential benefits of the recommendations to include improved access to appropriate management, particularly referral to palliative specialists. Improved symptom control and better end-of-life care. Reduced time spent in hospital and a better experience for carers. The GDG considered that potential harms were likely to be small but may include some morbidity from nerve block, chemotherapy and radiotherapy. The GDG considered that the substantial benefits were likely to outweigh the relatively small risk of potential harms.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic.

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	The GDG considered that the recommendations were likely to lead to increased nerve block, chemotherapy and radiotherapy costs, increased palliative care costs, and increased time from urological teams. The GDG balanced this against the potential savings from reduced time in hospital, reduced need for acute services, and a reduction in the use of pain relieving drugs. The GDG thought that there is likely to be a net saving to the NHS.
Other considerations	The GDG noted some concern that younger patients may currently get better access to nerve blocks. However, the recommendations aim to promote access and reduce inequality. The GDG were unsure as to the full extent of the change in practice required to implement the recommendations. However, they expected there to be a modest increase in the use of radiotherapy, nerve block and chemotherapy. The GDG also noted that the recommendations may increase awareness of end-of-life issues for urology patients and increase involvement for urology teams. The GDG considered existing NICE guidance on supportive and palliative care. The practicalities of how best to arrange palliative care/urology consultations for patients in the community, particularly in care homes, were also considered.

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Appendices

Appendix A: The cost-effectiveness of a single instillation of chemotherapy immediately after transurethral resection of bladder tumour

A.1 Background

Non-muscle invasive bladder cancer (NMIBC) tumours can be surgically removed using transurethral resection of bladder tumour (TURBT). However, these tumours are likely to return on the urothelium. This high risk of recurrence is a problem for patients because it raises the concern that the cancer will progress and so the patient will need to undergo further treatment (either another TURBT or diathermy).

The risk of recurrence can be reduced by the administration of chemotherapy medication into the bladder (intravesical chemotherapy), which can be done immediately, or shortly after TURBT. However, there are disadvantages to using intravesical chemotherapy as it is associated with some side effects and comes at an additional cost.

There is currently debate about which NMIBC patients should be treated with intravesical chemotherapy, including whether patients with small or very small tumours should be treated.

A.2 Aim of analysis:

To estimate the cost-effectiveness of a single instillation of intravesical chemotherapy in addition to TURBT in comparison to TURBT alone in patients with NMIBC.

A.3 Existing Economic Evidence

A systematic literature review was performed to assess the current economic literature in this area. The review identified 515 possibly relevant economic papers relating to bladder cancer. Of these, 50 full papers were obtained for appraisal. One paper was identified that related to the topic at hand; Green et al. 2013.

In the study, the authors utilised a decision analytic model to estimate the cost-effectiveness of a single instillation of chemotherapy given after a TURBT, with effectiveness estimated in terms of quality adjusted life years (QALYs). Thus, the study met the inclusion criteria as it was a relevant cost-utility analysis.

Green et al. 2013 sought to examine the cost-effectiveness of fulguration compared to TURBTs with and without perioperative intravesical chemotherapy in patients with low risk NMIBC. The authors concluded that fulguration without perioperative intravesical chemotherapy was the most cost-effective strategy for treating low-risk NMIBC. However, unusually, the authors based this conclusion upon individual cost-effectiveness calculations rather than the standard incremental calculations. When following the more standard cost-effectiveness methodology using incremental cost-effectiveness ratios (ICERs), it appears that perioperative intravesical chemotherapy plus fulguration would be the most cost-effective strategy. This strategy has an ICER of $4,169 per QALY, which is likely to fall below

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the cost-effectiveness threshold[k]. The authors also conducted sensitivity analysis, which showed that the effectiveness of perioperative intravesical chemotherapy and the cost of TURBT were likely to be key drivers of the cost-effectiveness result.

However, Green et al. 2013 can only be deemed partially applicable to the decision problem this guideline seeks to address. The analysis considered the US healthcare system, which differs substantially from the UK system. In addition, the study only partially addressed our decision problem as it only evaluated cost-effectiveness in low risk NMIBC patients, whereas we are interested in all NMIBC risk groups. Furthermore, some potential limitations were identified in the analyses with uncertainty over some of the input values that were utilised and some concerns over the interpretation of the results.

Overall, it was considered that the current economic literature was partially useful but further analysis would be required to robustly estimate the cost-effectiveness. It should also be noted that the existing economic literature was useful for informing the development of our own economic model.

A.4 De Novo Economic Model

Since the current economic literature didn't adequately address the decision problem[l], a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel. The basic model structure is shown in Figure 39.

[k] However, it should be noted that there is no official cost-effectiveness threshold used in the evaluation of treatments in the US health care system.

[l] It should be noted that, while none of the above studies met the requirements for inclusion in the systematic review, they were nonetheless informative in helping to develop our own de novo economic model.

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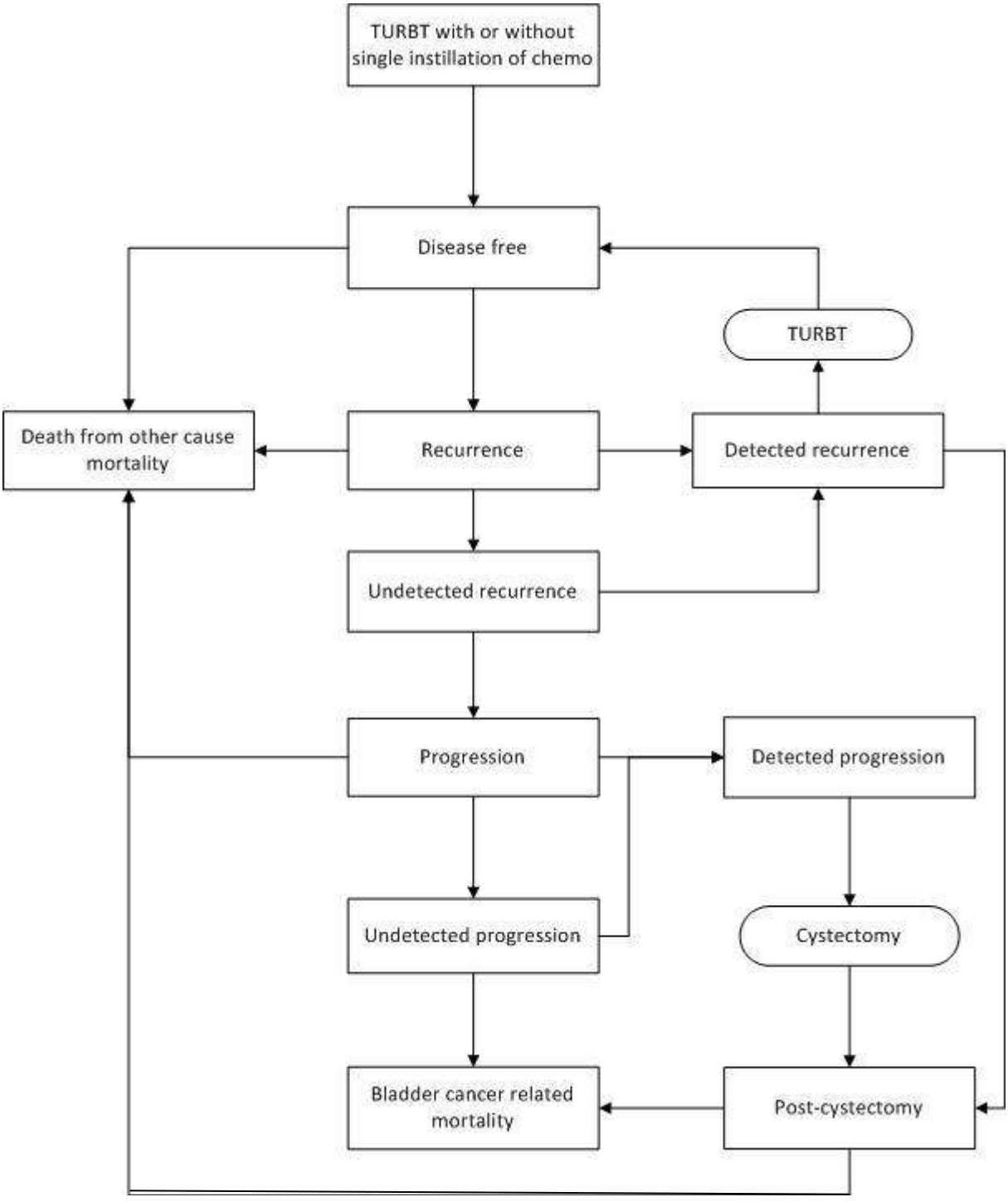
Figure 39: Basic model structure



The patient enters the model in a 'disease free' state following an initial transurethral resection of the bladder tumour (TURBT) with or without a single instillation of chemotherapy (depending upon modelled treatment arm). At each 3-monthly model cycle the patient may experience a bladder cancer recurrence. If the recurrence is detected, the patient will undergo a further TURBT (or fulguration of the tumour) and return to a disease free state. However, if the recurrence is not detected, then the patient will be at risk of progression and will have to undergo further treatment once this progression is eventually detected (cystectomy and possibly neo-adjuvant chemotherapy). The patient may also die from

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bladder cancer related mortality after experiencing progression and may die from other cause mortality from any health state.

Estimated total costs and quality adjusted life years (QALYs) are collected over the modelled 10 year time horizon for each follow-up strategy. The total costs will include all costs associated with initial treatment, surveillance, further treatment and management and are described in more detail in the cost section of this report. QALYs are calculated by multiplying the life years that patients spend in each health state by the associated quality of life (QoL) weighting, which represent the patient's valuation of their health state. QALYs and QoL values are discussed in more detail in later sections of the report.

Future costs and benefits were discounted at a rate of 3.5% per year as recommended by NICE.

A.4.1 Natural history of disease - risk of recurrence and progression

The risk of recurrence and progression in patients with NMIBC was estimated using risk equations based on an analysis of 2,596 patients from seven EORTC[m] trials (Sylvester et al. 2006). Patients are 'scored' based on a number of risk factors, such as number of tumours, tumour size, prior recurrence rate, T category, presence of CIS and grade. The scores associated with the risk factors are shown in table 158.

Table 158: EORTC scores associated with risk factors

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2 to 7	3	3
≥ 8	6	3
Tumour size		
< 3cm	0	0
≥ 3cm	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 rec/yr	2	2
> 1 rec/yr	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total risk score	**0-17**	**0-23**

The overall recurrence and progression risk scores computed from the above table have an associated one year and five year risk of recurrence and progression. The one year and five year risks of recurrence and progression are shown in tables 159 and 160.

[m] European Organisation for Research and Treatment of Cancer

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Table 159: EORTC recurrence probabilities for recurrence score groups

Recurrence score	1 year probability of recurrence	5 year probability of recurrence
0	**15.0%** (10%, 19%)	**31.0%** (24%, 37%)
1 - 4	**24.0%** (21%, 26%)	**46.0%** (42%, 49%)
5 – 9	**38.0%** (35%, 41%)	**62.0%** (58%, 65%)
10 – 17	**61.0%** (55%, 67%)	**78.0%** (73%, 84%)

Table 160: EORTC recurrence probabilities for recurrence score groups

Progression score	1 year probability of progression	5 year probability of progression
0	**0.2%** (0%, 0.7%)	**0.8%** (0%, 1.7%)
2 – 6	**1.0%** (0.4%, 1.6%)	**6.0%** (5%, 8%)
7 – 13	**5.0%** (4%, 7%)	**17.0%** (14%, 20%)
14 – 23	**17.0%** (10%, 24%)	**45.0%** (35%, 55%)

For the purposes of the economic model, it was necessary to convert these five year and one year risks into 3-monthly risks to match the model cycle length used. In order to capture the higher risk of recurrence and progression in the first year, separate 3 monthly risks were used in the first year and in subsequent years (based on the one year risk and five year risk, respectively).

The EORTC risk equations consider recurrence and progression *independently* but, for the purposes of this analysis, a relationship between recurrence and progression was assumed. This relationship was estimated from the EORTC data by calculating the *probability of progression given recurrence* in each of the risk groups.

Note that the risk group classifications used in clinical practice do not translate neatly to any one set of recurrence and progression risk. There are multiple permutations of recurrence and progression risk that are possible in each of the clinical risk groups as shown in table 161

Table 161: Recurrence and progression risk scores for each risk group variant

Clinical risk group	Recurrence score	Progression score	Example
Low risk			
Base case values	0	0	Solitary tumour, <3cm, Ta, G1
Variant 1	1-4	0	Solitary tumour, <3cm, Ta, G2
Intermediate risk			
Base case values	1-4	2-6	Solitary tumour, >3cm, Ta, G1
Variant 1	5-9	2-6	2-7 tumours, >3cm, Ta, G1
Variant 2	10-17	7-13	>8 tumours, >3cm, T1, G1
High risk			
Base case values	10-17	14-23	>8 tumours, >3cm, T1, G3
Variant 1	5-9	7-13	Solitary tumour, >3cm, Ta, G3
Variant 2	5-9	14-23	2-7 tumours, >3cm, T1, G3
Variant 3	10-17	7-13	>8 tumours, >3cm, T1, G2

In the base case analysis, the recurrence and progression risk combinations that are likely to best reflect the majority of patients within each clinical risk group were selected. Variations in the recurrence and progression score are assessed in sensitivity analysis. Table 162 shows

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the three monthly risks of recurrence, progression and progression given recurrence applied for each of the risk groups in the base case analysis.

Table 162: Three monthly recurrence and progression risk applied in the model

Outcome	3 monthly rates		
	Recurrence	Progression given recurrence	Progression
First year			
Low risk	3.98%	1.26%	0.05%
Intermediate risk	6.63%	3.78%	0.25%
High risk – Lower	11.26%	11.31%	1.27%
High risk – Upper	20.97%	21.70%	4.55%
Subsequent years			
Low risk	1.84%*	2.18%*	0.04%*
Intermediate risk	3.03%	10.18%	0.31%
High risk – lower	4.72%	19.64%	0.93%
High risk – upper	7.29%	40.39%	2.94%

**In low risk patients, rates of recurrence and progression in years 6-10 are assumed to be zero*

Note that since the modelled time horizon of 10 years exceeds the predicted risk estimates from the EORTC trials (5 years), it was also necessary to make some assumptions about the risk profile of patients in years 5-10. In the base case, it was assumed that the estimated subsequent year rate (i.e. years 2-5) would be maintained in years 6-10 except in the case of low-risk patients in whom it was assumed that risk would be zero after 5 years (reflecting the clinical practice of discharging low-risk patients from follow-up protocols after 5 years).

It should also be noted that, in accordance with the EORTC risk scores, modelled low risk and intermediate risk patients that experience a recurrence will thereafter be subject to the higher risk of recurrence and progression associated with the risk level above. For example, low risk patients that have a recurrence are thereafter subject to the recurrence and progression risk scores associated with intermediate risk patients. However, there are nuances to this increased risk which cannot be accurately captured in the model as it does not model changes in tumour characteristics directly. For example, it is not always the case that a recurrence would place an intermediate risk patient into a higher risk group as it would depend on the patient's initial score.

A.4.2 Key clinical effectiveness data

A.4.2.1 Effectiveness of single instillation of chemotherapy

The key effectiveness data utilised in the model is the reduction in recurrence risk associated with a single instillation of intravesical chemotherapy following a TURBT. According to the systematic review of the clinical evidence, the use of a single instillation of intravesical chemotherapy in addition to TURBT has a relative risk of 0.67 in comparison to TURBT alone. This treatment effect was assumed to last for two years reflecting the general consensus around its possible duration. Thereafter, the risk of recurrence was assumed to be equal to that with TURBT only. In addition, the treatment effect is not assumed to affect future recurrences if the patient has a recurrence during the two years after the single chemotherapy instillation.

Note that the single instillation of chemotherapy does not directly reduce the rates of progression. This is in line with the evidence base, which suggests that there is no treatment effect on the rates of progression. However, it should be noted that because of the model structure, a lower rate of recurrences would lead to a lower rate of progression because

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progression is dependent upon recurrence. Therefore, an indirect treatment effect on progression is essentially included in the model. This assumption is relaxed in a sensitivity analysis where the rates of recurrence and progression are assumed to be independent.

A.4.2.2 Treatment related morbidity

No comparative data on morbidity were identified in the systematic review of the clinical evidence. However a meta-analysis (Sylvester 2004) of seven trials suggested that mild irritative bladder symptoms (including dysuria, frequency and macroscopic haematuria) would occur in approximately 10% of patients treated with a single post-operative dose of intravesical chemotherapy. In addition, allergic skin reactions were reported in 1-3% of patients in two studies.

Since no data were available on morbidity in patients treated with TURBT, it was conservatively assumed that 5% would have irritative bladder symptoms and there would be no skin reactions. The treatment related morbidity rates applied in the model are shown in table 163.

Table 163: Treatment related morbidity rates applied in the model

	Occurrence rate		
Morbidity event	**Value**	**PSA distribution**	**Source**
TUR alone			
Irritative bladder symptoms	5.0%	Beta (alpha = 5, beta =95)	GDG assumption
Skin reactions	0.0%	Not varied	GDG assumption
TURBT + Single instillation of chemotherapy			
Irritative bladder symptoms	10.0%	Beta (alpha = 10, beta = 90)	Sylvester et al. 2004
Skin reactions	3.0%	Beta (alpha = 3, beta = 97)	Sylvester et al. 2004

A.4.2.3 Follow-up test diagnostic accuracy data

The diagnostic accuracy data for flexible cystoscopy (sensitivity and specificity) that was applied in the model are shown in table 164. The data were sourced from the systematic review of the clinical evidence conducted for this guideline, with most data being sourced from a systematic review by Mowatt et al. 2010.

Table 164: Diagnostic accuracy of flexible cystoscopy

Diagnostic test	Value	PSA distribution	Source
Sensitivity	71%	Beta (alpha = 71, beta = 29)	Systematic review
Specificity	72%	Beta (alpha = 72, beta = 28)	Systematic review

A.4.2.4 Bladder cancer related mortality

Bladder cancer related mortality rates were estimated using data identified in the systematic review of the clinical evidence. A systematic review by Van den Bosch et al. 2011 was utilised, which estimated survival rates in high risk NMIBC patients that have progressed to MIBC. In the report, the assumption was made that patient that die from bladder cancer must first progress to muscle invasive disease and then to metastatic cancer. The same assumption was made in the economic model.

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Van den Bosch et al. 2011 reported a disease specific survival rate of 35% in NMIBC patients that have undergone a cystectomy and experienced progression over a median follow-up time of 48-123 months. This was converted to an estimated 3 monthly disease specific mortality rate of 3.6% in patients that have progressed to MIBC in the model. In NMIBC patients, the estimated disease specific mortality rate applied in the model was 0.5%. This lower rate reflects that patients would have to first progress to MIBC before dying of bladder cancer (based on the 21.3% progression rate reported in Van den Bosch et al. 2011).

It should also be noted that patients with undetected progression are assumed to be subject to the mortality rate associated with MIBC.

A.4.2.5 Other cause mortality

Death from other causes was captured using 2009-2011 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. In the base case, the model was run with an average age of 60 and was assumed to be 50% female (note that these parameters only influence other cause mortality in the model). The annual probabilities of other mortality were converted to three-monthly probabilities for use in the model.

A.4.3 Cost data

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. GP visit). Where possible, all costs were estimated in 2012-13 prices.

The majority of costs were sourced from NHS reference costs 2012/13 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dosages from the British National Formulary (BNF) and unit cost information from the electronic market information tool (eMit). Where unit costs for drugs were not available from eMit, prices from the BNF were used. Resource use and cost information were obtained from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

Costs for each aspect of the treatment pathway are detailed in the relevant sections below.

A.4.3.1 Cost of initial TURBT and single instillation of chemotherapy

The cost of a TURBT was estimated to be £1,267.59, which was based on the cost of an 'Intermediate Endoscopic Bladder Procedure' from NHS reference costs. The cost of delivering the single instillation of chemotherapy is dependent upon the setting in which it is given; in theatre or ward. If it is given in the theatre then the delivery cost will be the cost of using the Mito-In system (estimated to be £4.00) and the surgical consultant time (£4.67). Whereas, if it is delivered by a nurse then the costs incurred will be the cost of an advanced nurse consultation (includes clinical nurse specialist), the cost of the Mito-in system and the additional costs of gloves, syringes and other sundries (estimated to be around £6.50) (Table 165).

In the base case it was assumed that intravesical chemotherapy was delivered immediately after surgery in theatre in 25% of cases with the remaining 75% delivered later by a nurse.

Table 165: Initial TURBT and single instillation costs

Therapy	Cost	PSA distribution	Source
WLC-assisted TURBT	£1,267.59	Gamma (SE =333.97, alpha = 14, beta = 88)	NHS ref costs 12-13

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Therapy	Cost	PSA distribution	Source
Cost of a single instillation of chemotherapy			
Drug cost			
Mitomycin C (per 40mg vial)	£79.88	Gamma (SE = 59.21, alpha = 2, beta = 44)	British National formulary (BNF)
Delivery cost			
In Theatre (25% of patients)			
Mito-In system	£4.00	Gamma (SE =2.97, alpha = 2, beta =2)	GDG estimate
Surgical consultant time (based on GDG estimate of 2 minutes)	£4.67	Gamma (SE =3.46, alpha = 2, beta =3)	Unit costs of health and social care 2012
Ward (75% of patients)			
Mito-In system	£4.00	Gamma (SE =2.97, alpha = 2, beta =2)	GDG estimate
Advanced nurse consultation	£22.00	Gamma (SE = 16.31, alpha = 2, beta = 12)	Unit costs of health and social care 2012
Additional costs of delivering intravesical chemotherapy (sundries)	£6.50	Gamma (SE =4.82, alpha = 2, beta = 4)	GDG estimate

A.4.3.2 Adverse event costs

The GDG felt that, in most instances, there would not be any additional costs associated with the treatment related morbidity that could be experienced as no treatment would be administered. However, it was thought that antihistamines and antibiotics were sometimes used to treat a skin rash and irritative bladder symptoms, respectively. Thus, we conservatively assumed (i.e. biasing against the intervention being tested) that all irritative bladder symptoms and skin reactions would be treated, with the drugs being prescribed after a consultation with the urologist (cost of 'Non-admitted face to face attendence, follow-up in Urology' from NHS reference costs). The treatment related morbidity costs applied in the model are detailed in table 166.

Table 166: Adverse event costs

Event	Drug and dose	Cost	PSA distribution	Source
Irritative bladder symptoms	Co-amoxiclav 625mg, 3 times daily for5 days	£1.13	Gamma (SE =0.56, alpha = 4, beta = 0)	Electronic market information tool (eMit)
Skin reactions	Chlorphenamine 4mg, 4 times daily for 5 days	£0.16	Gamma (SE = 0.06, alpha = 6, beta = 0)	eMit
Urologist consultation	N/A	£94.11	Gamma (SE = 28.41, alpha = 11, beta = 9)	NHS Reference costs 2012-13

A.4.3.3 Follow-up costs

Post resection follow-up

Following the initial resection, patients were assumed to be followed up in the manner that best reflects current practice. However, there is variation in current practice and the strategy most commonly used is not definitively known. The GDG adjudged that the strategies described by Hall et al. 1994 best reflect current practice and so these were used in the analysis. The strategies are summarised in table 167 for each risk group:

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Table 167: Current practice follow-up strategies

Risk group	Follow-up strategy
Low risk	Cystoscopy at 3 months, 1 year and annually thereafter
Intermediate risk	Cystoscopy every 3 months for 2 years, then every 6 months for 2 years and annually thereafter
High risk	Cystoscopy every 3 months for 2 years, then every 6 months for 2 years and annually thereafter

The cost of a flexible cystoscopy applied in the model was £401.88, which was based upon the cost of a "Diagnostic Flexible Cystoscopy, 19 years and over" as a day case procedure from NHS reference costs. However, there is variation in current practice as to whether cystoscopies are coded as an outpatient or day case procedure. Day case procedures were thought to be more common and thus were selected for the base case analysis but the cost associated with flexible cystoscopies given as outpatient procedures (£164.00) was applied in a sensitivity analysis.

The consequences of cystoscopic inaccuracy should also be noted. True negative and false negative results would only incur the cost of the initial investigation itself whereas true positive and false positive results would incur the cost of the initial investigation and the cost of performing a biopsy ('unnecessarily' in the case of false positive patients, at which point the error would be realised).

A.4.3.4 Recurrence costs

The costs associated with treating recurrences are shown in table 168.

Table 168: TURBT and diathermy costs used to treat recurrences

Therapy	Value	PSA distribution	Source
Proportion			
TURBT	33%	Beta (alpha = 33, beta = 67)	Estimate from GDG
Diathermy	67%	1 – TURBT proportion PSA value	Estimate from GDG
Cost			
TURBT	£1,267.59	Gamma (SE =333.97, alpha = 14, beta = 88)	NHS ref costs 12-13
Diathermy	£401.88	Gamma (SE =158.85, alpha = 6, beta = 63)	NHS ref costs 12-13

Patients that have a recurrence would need further treatment; either another TURBT or diathermy in assumed proportions of 33% and 67%, respectively. The cost of a TURBT was estimated to be £1,267.59, which was based on the cost of an 'Intermediate Endoscopic Bladder Procedure' from NHS reference costs. The cost of diathermy was estimated to be equivalent to the cost of a flexible cystoscopy (£401.88 from NHS reference costs).

A.4.3.5 Further treatment costs

Mitomycin C course

Patients with intermediate risk bladder cancer are assumed to receive a course of Mitomycin C (once weekly for 6 weeks) at a cost of £479.28 (sourced from the BNF). The cost of administering Mitomycin C was obtained from NHS reference costs 2012/13 ('Introduction of Therapeutic Substance into Bladder' – LB17Z). In clinical practice, the therapy is either delivered as an outpatient or day case procedure. Thus, a weighted average cost was calculated based on the number of outpatient and day case admissions listed in NHS reference costs (57% were day case and 43% were outpatient). The average weighted cost of delivering Mitomycin C was estimated to be £220.74 per instillation.

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In current clinical practice, some low risk patients may receive a course of Mitomycin c following a recurrence. To capture this in the model it was assumed that 50% of low risk patients would receive a course of Mitomycin C after a recurrence. This assumption was informed by the clinical opinion of the GDG.

Bacillus Calmette-Guérin (BCG) therapy

Patients with high risk bladder cancer and initially low and intermediate risk patients that have had multiple recurrences are assumed to receive Bacillus Calmette-Guérin (BCG) therapy. These patients will first receive induction BCG therapy, which consists of six doses of BCG given once a week over a six week period. After a six week off-period, patients that have not had a recurrence or progression will then go onto receive maintenance BCG therapy. This consists of a further three doses given once a week over a three week period at six monthly intervals for a maximum of three years.

Patients that progress to muscle invasive disease while receiving BCG therapy are classed as 'BCG failures' and are assumed to undergo a cystectomy. In addition, in an attempt to reflect the clinical practice of classifying high risk recurrences as BCG failures, it has been assumed that a proportion of recurrences in patients receiving BCG therapy would be BCG failures. In high risk patients it is assumed that 50% of patients with a first recurrence and all patients with two recurrences on BCG therapy would be classed as BCG failures. In low and intermediate risk patients it is assumed that 50% of patients with a first or second recurrence and all patients with three recurrences on BCG therapy would be classed as BCG failures.

The cost of the BCG therapy is based on the average cost of ImmuCyst and OncoTICE with costs sourced from the BNF. The cost of delivering BCG was estimated to be £220.74 and was based on the same NHS reference cost codes used for the MMC course (see above).

The costs associated with bladder instillations (Mitomycin c and BCG) are shown in table 169.

Table 169: Intravesical instillation costs – Mitomycin C and BCG courses

Therapy	Value	PSA distribution	Source
Bladder instillation costs			
Delivery cost – day case	£285.78	Gamma (SE = 107.66, alpha = 7, beta = 41)	NHS ref costs 12-13 -LB17Z
Delivery cost – outpatient	£133.57	Gamma (SE =46.92, alpha = 8, beta = 16)	NHS ref costs 12-13 -LB17Z
Proportion delivered as day case	57%	Beta (alpha = 57, beta = 43)	NHS ref costs 12-13 -LB17Z
Proportion delivered as outpatient	43%	1 – day case proportion	NHS ref costs 12-13 -LB17Z
Average delivery cost	£220.74	-	-
MMC Course			
Mitomycin C drug costs (once weekly for 6 weeks)	£479.28	Gamma (SE =355.29, alpha = 2, beta = 263)	BNF
Mitomycin C delivery cost	£1,324.42	-	-
BCG therapy			
Induction drug cost (6 doses)	£452.52*	Gamma (SE =335.45, alpha = 2, beta = 249)	BNF
Induction BCG delivery cost	£1,324.42	-	-

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Therapy	Value	PSA distribution	Source
Maintenance drug cost (3 doses, every 6 months)	£226.26†	Gamma (SE =167.72, alpha = 2, beta = 124)	BNF
Maintenance BCG delivery cost	£662.21	-	-

**Based on the average cost of 6 doses of ImmuCyst® (£475.38) and OncoTICE® (£429.66) †Based on the average cost of 3 doses of ImmuCyst® (£237.69) and OncoTICE® (£214.83)*

Cystectomy and neo-adjuvant chemotherapy

Patients that progress to muscle invasive disease or experience BCG failure are assumed to undergo a cystectomy. The cost associated with a cystectomy was estimated to be £9,538.29 based on the cost of a 'Cystectomy with Urinary Diversion and Reconstruction, with CC Score 0-2' from NHS reference costs.

It was further assumed that 80% of patients undergoing a cystectomy would receive neo-adjuvant chemotherapy. In current clinical practice the majority of patients receiving neoadjuvant chemotherapy receive a regimen of gemcitabine and cisplatin (GemCis) but a minority also receive accelerated MVAC (methotrexate, vinblastine, adriamycin and cisplatin). The proportion of patients receiving each regimen in the model was based on the clinical opinion of the GDG, with 90% receiving GemCis and 10% receiving accelerated MVAC.

Chemotherapy drug costs were estimated using unit costs from the BNF with doses and schedules as recommended by the GDG. Drug doses were estimated using an average body surface area of 1.91m^2 for men and 1.71m^2 for women as reported in a study by Sacco et al. 2010. In addition to the drug costs, the costs associated with delivering chemotherapy were also captured using tariffs from NHS reference costs, which vary depending upon the complexity of delivering the chemotherapy (principally the time required to deliver the chemotherapy). In the case of accelerated MVAC, patients also receive the G-CSF, Pegylated filgrastim at a cost of £686.38 for a 6mg prefilled syringe.

The costs per cycle of chemotherapy are shown in table 170 for a schedule of GemCis and accelerated MVAC. Patients receiving neoadjuvant chemotherapy are assumed to receive three cycles of chemotherapy as recommended by the GDG.

Table 170: Chemotherapy cost per cycle of GemCis and accelerated MVAC

Therapy	Value	PSA distribution	Source
GemCis			
Proportion of patients receiving GemCis	90%	Beta (alpha = 90, beta = 10)	Assumption
Initial chemotherapy delivery cost*	£267.99	Gamma (SE = 91.36, alpha = 9, beta =31)	NHS reference costs 2012/13 - SB13Z
Deliver subsequent elements of a chemo	£301.56	Gamma (SE = 108.07, alpha = 8, beta = 39)	NHS reference costs 2012/13 - SB15Z
Gemcitabine (1000mg/m2 on days 1,and 8)	£46.02	Gamma (SE = 383.42, alpha = 2, beta = 284)	Unit costs from eMit
Cisplatin (70mg/m2 on day 2)	£21.49	Gamma (SE = 48.16, alpha = 2, beta = 36)	Unit costs from eMit
Total GemCis cost per cycle	*£637.05*	-	-
Accelerated MVAC			
Proportion of patients receiving MVAC	10%	1 – proportion receiving GemCis	Assumption

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Therapy	Value	PSA distribution	Source
Initial chemotherapy delivery cost†	£329.80	Gamma (SE = 146.63, alpha = 5, beta = 65)	NHS reference costs 2012/13 - SB14Z
Administration of Pegfilgrastim by district nurse*	£35.00	Gamma (SE = 25.95, alpha = 2, beta = 19)	Unit costs of health and social care 2013
Methotrexate (30 mg/m2 given on day 1)	£7.04	Gamma (SE = 27.89, alpha = 2, beta = 21)	Unit costs from eMit
Vinblastine (30 mg/m2 given on day 1)	£6.56	Gamma (SE = 5.27, alpha = 2, beta = 4)	Unit costs from eMit
Adriamycin (30 mg/m2 given on day 1)	£5.28	Gamma (SE = 78.37, alpha = 2, beta = 58)	Unit costs from eMit
Cisplatin (70mg/m2 on day 1)	£21.49	Gamma (SE = 48.16, alpha = 2, beta = 36)	Unit costs from eMit
Pegfilgrastim (6 mg prefilled syringe on day 2 or 3)	£686.38	Gamma (SE = 508.81, alpha = 2, beta = 377)	Unit costs from BNF
Total cost per cycle	*£1,091.54*	-	-

**Deliver more complex parenteral chemo at 1st attendance †Deliver Complex Chemo, including Prolonged Infusional Treatment, at 1st Attendance*

Post cystectomy follow-up

Patients that have undergone a cystectomy are assumed to be followed up in the manner reflecting current practice with a combination of urological consultations, urethroscopies, CT scans and blood tests (kidney function and PSA). The patient is assumed to be followed up by the urological consultant at three, six and twelve months and annually thereafter at a cost of £94.11 per consultation based on the cost of a 'Non-admitted face to face attendence, follow-up in Urology' from NHS Reference Costs. Urethroscopies are assumed to be used annually at an estimated cost of £672.53, based on the cost associated with a 'Minor or Intermediate Urethra Procedure, 19 years and over' as a day case procedure from NHS Reference Costs. CT scans are assumed to be used on a six monthly basis for the first year and annually thereafter at a cost of £83.85 (NHS Reference Costs). Blood tests are assumed to be done on a six monthly basis at an assumed cost of £20.00. The follow-up costs applied in the model are shown in table 171.

Table 171: Post-cystectomy follow-up costs

Therapy	Cost	PSA distribution	Source
Urethroscopy	£672.53	Gamma (SE = 214.43, alpha = 10, beta = 68)	NHS ref costs 12-13
CT Scan	£83.85	Gamma (SE = 25.15, alpha = 11, beta = 8)	NHS ref costs 12-13
Blood tests (kidney and PSA tests)	£20.00	Gamma (SE = 14.83, alpha = 2, beta = 11)	GDG assumption
Clinical follow-up (urology consultant)	£94.11	Gamma (SE = 28.41, alpha = 11, beta = 9)	NHS ref costs 12-13

Systemic chemotherapy and palliative care

A metastatic bladder cancer state was not explicitly modelled as such. However, it was assumed that patients that die from bladder cancer related mortality after progressing to muscle invasive disease were likely to have developed metastatic disease. Thus, the costs associated with treating metastatic disease as well as the cost of palliative care were applied to these patients.

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It was assumed that the patient would have received systemic chemotherapy, which, as was the case in neoadjuvant chemotherapy, was assumed to be either GemCis or accelerated MVAC in assumed proportions of 90% and 10%, respectively. The chemotherapy doses were the same as in the neoadjuvant setting and so the cost per cycle is the same as in the table above for neoadjuvant chemotherapy. However, more cycles of chemotherapy are administered in systemic chemotherapy with patients assumed to receive six cycles of chemotherapy (based on the advice of the GDG).

The cost of palliative care in bladder cancer patients was sourced from a report on deaths from urological cancers in England, 2001-10 by the National End of Life Care Intelligence Network. The palliative care cost was estimated to be £8,502, based on an average length of stay of 11.4 days and an average of 3.1 admissions.

A.4.4 Health-related quality of life data

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs are estimated by combining the life year estimates with utility values (or QOL weights) associated with being in a particular health state. These utility values were identified through a search of the available literature.

There is a paucity of high quality of life (QoL) data available in bladder cancer. In particular, there is a shortage of data on patients with NMIBC with most of the available QoL data focusing on post-cystectomy patients. However, it is recognised that QALYs need to be estimated in order to assess cost-effectiveness using the thresholds employed by NICE (£20,000 - £30,000 per QALY) and thus it is useful to utilise QoL data, even if they are of relatively poor quality. It is however recognised as a limitation of the analysis and the QoL values were subjected to sensitivity analysis to assess how influential they are on the final decision.

For the purposes of this economic evaluation, the following QoL data were utilised (Table 172).

Table 172: Health related quality of life weights

Health state	Utilities	PSA distribution	Source
Monitoring	0.780	Beta (alpha = 78, beta = 22)	Mowatt et al. 2010
Post-cystectomy	0.743	Beta (alpha = 74, beta = 26)	Kulkarni et al. 2007
Metastases with systemic chemo	0.600	Beta (alpha = 60, beta = 40)	Kulkarni et al. 2007
Decrements			
TURBT at first recurrence	0.033	Beta (alpha = 3, beta = 97)	SF-36 values from Yoshimura et al. 2005 converted to EQ-5D using mapping algorithm from Ara et al. 2008
TURBT at subsequent recurrence	0.057	Beta (alpha = 6, beta = 94)	
TURBT to detect progression	0.033	Beta (alpha = 3, beta = 97)	

The baseline QoL for patients undergoing monitoring for bladder cancer recurrence (after an initial TURBT) was estimated to be 0.78. This value was sourced from a HTA by Mowatt et al. 2010.

A decrement was utilised for patients that underwent treatment for a bladder cancer recurrence. This was estimated using a study by Yoshimura et al. 2005 that measured QoL

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in patients with superficial bladder cancer that underwent TURBT. This study measured quality of life using the Short-Form 36-item survey (SF-36), which is not the measure preferred by NICE. Therefore, a mapping algorithm by Ara et al. 2008 was utilised to convert the SF-36 data into EuroQol 5-dimension (EQ-5D) data (the measure preferred by NICE). Using this methodology, the QoL decrement for a bladder cancer recurrence was estimated to be 0.033 for a primary recurrence and 0.057 for a subsequent recurrence.

QoL values for patients in a post-cystectomy state and a metastatic state with palliative care (0.743 and 0.600, respectively) were sourced from a health economic study by Kulkarni et al. 2007

Note that, in the base case, it was assumed that there would be no further QoL decrements associated with irritative bladder symptoms or skin reactions. This assumption was made after discussion with the GDG and, in particular, the patient representatives, who felt that the QoL impact of these side effects would be negligible when considering the QoL decrement associated with TURBTs themselves. However, this assumption was relaxed in sensitivity analysis where QoL decrements were applied for treatment-related adverse events.

A.4.5 Sensitivity analysis

To estimate uncertainty and determine the key drivers of the model, a series of one-way sensitivity analysis were conducted. One-way sensitivity analysis involves changing one input parameter, re-running the model and recording and interpreting the new cost-effectiveness result.

To further estimate uncertainty in the model, probabilistic sensitivity analysis was performed. Probabilistic sensitivity analysis involves running a series of simulations where the values of the model's input parameters are randomly sampled from a distribution around their mean value. This analysis is useful for assessing the uncertainty around all parameter values simultaneously.

The standard errors, distribution type and distribution parameters (alpha and beta values) used to inform the distributions used in the probabilistic sensitivity analysis are shown in each of the input tables in this report. Where possible, the PSA distributions were informed by the standard deviations or standard errors reported in the study or data source. Where data on uncertainty were not available, the distribution parameters were estimated by assuming that the upper and lower quartiles were equal to ±50% of the mean value.

Note that, in general, gamma distributions were used for cost inputs, beta distributions were used for utility values and probabilities, dirichlect distributions were used for conditional variables and normal distributions were used for all other variables.

A.4.6 Results

The results of the economic model are presented as expected costs and QALYs for intervention along with an incremental cost-effectiveness ratio (ICER) for each comparison. The ICER is used to measure the cost-effectiveness of one intervention over another; it is calculated as shown in figure 40.

Figure 40: Calculation of the incremental cost-effectiveness ratio (ICER)

$$\text{ICER} = (\Delta \text{ Cost}) / (\Delta \text{ QALYs})$$

$$\text{ICER} = (\text{Cost Intervention A} - \text{Cost Intervention B}) / (\text{QALYs Intervention A} - \text{QALYs Intervention B})$$

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It can be seen that by dividing the difference in costs of each intervention by the difference in benefits (in QALY terms), a cost per QALY can be calculated for each comparison. NICE typically has a threshold of £20,000 for one additional QALY gained. Thus, an intervention with ICER < £20,000 can usually be considered cost-effective. Interventions with ICER values above £30,000 are not typically considered cost-effective. For ICER values between £20,000 and £30,000, an intervention may be considered cost-effective if it is associated with significant benefits.

The model was run over a time horizon of ten years as this was expected to be the time period over which the outcomes were most likely to differ for patients undergoing each of the follow-up strategies.

A.4.6.1 Base case results

The base case results of the analysis are presented in table 173 for patients in each risk category. It can be seen that, in every risk category, a strategy of TURBT plus a single instillation of chemotherapy is more effective than a strategy of TURBT alone.

In the case of low and intermediate risk patients, it can also be seen that the addition of a single instillation of chemotherapy is cost saving over the modelled time horizon. This shows that the initial additional costs associated with the single chemotherapy instillation are outweighed by the cost savings associated with a reduction in recurrences (recurrence reductions of 17% and 10% were estimated over the modelled time horizon in the low and intermediate risk groups, respectively). Therefore in low and intermediate risk patients, a single instillation of chemotherapy can be considered dominant i.e. more effective and cost saving.

However, in the case of high risk patients, it can be seen that this is not the case. In high risk patients, the single instillation of chemotherapy is more costly than TURBT alone, suggesting that the potential cost savings are not as large in this group. However, it can also be seen that the addition of a single chemotherapy instillation provides an additional QALY at a cost of £6,432 and thus would be considered cost-effective using the NICE threshold (i.e. <£20,000 per QALY).

Table 173: Base case results of the model

	Cost		QALYs		
Treatment strategy	**Total**	**Incremental**	**Total**	**Incremental**	**Cost per QALY**
Low risk					
TUBRT alone	£8,850	-	6.29	-	-
TURBT + single chemo instillation	£8,203	-£647	6.30	0.0056	Dominant
Intermediate risk					
TUBRT alone	£21,992	-	6.20	-	-
TURBT + single chemo instillation	£21,191	-£801	6.22	0.0185	Dominant
High risk					
TUBRT alone	£27,679	-	5.52	-	-
TURBT + single chemo instillation	£28,069	£389	5.58	0.0605	£6,432

A.4.6.2 Risk score variants

As mentioned in an earlier section of the report, the EORTC risk equations suggest that multiple permutations of recurrence and progression risk are possible within each clinical risk group. For the base case analysis (above) the recurrence and progression risk combinations that were thought to best reflect the majority of patients were used. Table 174 shows the cost-effectiveness results using alternative combinations of recurrence and progression risk for low, intermediate and high risk patients.

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Table 174: Cost-effectiveness results using variants on the clinical risk groups

Follow-up strategy	Cost		QALYs		Cost per QALY
	Total	Incremental	Total	Incremental	
Low risk					
Variant 1 (recurrence score of 1-4 , progression score of 0)					
TUBRT alone	£10,914	-	6.29	-	-
TURBT + single chemo instillation	£9,996	-£918	6.29	0.0067	Dominant
Intermediate risk					
Variant 1 (recurrence score of 5-9, progression score of 2-6)					
TUBRT alone	£24,652	-	6.16	-	-
TURBT + single chemo instillation	£23,796	-£855	6.19	0.0245	Dominant
Variant 2 (recurrence score of 10-17, progression score of 7-13)					
TUBRT alone	£26,835	-	6.09	-	-
TURBT + single chemo instillation	£26,130	-£705	6.12	0.0260	Dominant
High risk					
Variant 1 (recurrence score of 5-9, progression score of 7-13)					
TUBRT alone	£26,597	-	5.83	-	-
TURBT + single chemo instillation	£26,611	£14	5.88	0.0543	£259
Variant 2 (recurrence score of 5-9, progression score of 14-23)					
TUBRT alone	£26,990	-	5.59	-	-
TURBT + single chemo instillation	£27,006	£17	5.65	0.0661	£250
Variant 3 (recurrence score of 10-17, progression score of 7-13)					
TUBRT alone	£27,390	-	5.72	-	-
TURBT + single chemo instillation	£27,771	£381	5.78	0.0629	£6,053

It can be seen that, despite changes in the cost, QALY and ICER values, the conclusions regarding cost-effectiveness are unchanged from the base case analysis. In low and intermediate risk patients, TURBT plus a single instillation of chemotherapy is still dominant i.e. more effective and cost saving. In high risk patients, TURBT plus a single instillation of chemotherapy is still more effective and expensive than TURBT alone and it remains cost-effective in all risk variants.

A.4.7 One-way sensitivity analysis

Table 175 shows the results of a range of one-way sensitivity analyses that were conducted.

Table 175: One-way sensitivity analysis results

Change made	Cost-effectiveness result (ICER)		
	Low risk	Intermediate risk	High risk
Chemotherapy given in theatre	Dominant	Dominant	£6,137
Chemotherapy given on the ward	Dominant	Dominant	£6,531
NHS reference cost used for single instillation	Dominant	Dominant	£9,640
No discounting	Dominant	Dominant	£9,201
Only TURBTs used to treat recurrences	Dominant	Dominant	£9,012
Only diathermy used to treat recurrences	Dominant	Dominant	£5,118
No TURBT utility decrements	Dominant	Dominant	£6,447
No AE treatment costs	Dominant	Dominant	£6,307
No AEs in TURBT arm	Dominant	Dominant	£6,511

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Change made	Cost-effectiveness result (ICER)		
	Low risk	Intermediate risk	High risk
AE disutilities of 0.01 included	Dominant	Dominant	£6,454
AE disutilities of 0.05 included	Dominant	Dominant	£6,540
Single chemo instillation effect lasts 3 months	Dominant	Dominant	£17,890
Single chemo instillation effect lasts 6 months	Dominant	Dominant	£14,008
Single chemo instillation effect lasts 1 year	Dominant	Dominant	£8,944
Single chemo instillation effect lasts 1.5 years	Dominant	Dominant	£7,780
Cystoscopy sensitivity = 100%	Dominant	Dominant	£13,172
Cystoscopy specificity = 100%	Dominant	Dominant	£1,935
Assume cystoscopy is perfect test†	Dominant	Dominant	£6,314
Upper relative risk estimate (=0.79)	Dominant	Dominant	£7,931
Lower relative risk estimate (=0.56)	Dominant	Dominant	£5,666

† Assumes cystoscopy sensitivity = 100% and specificity = 100%

Table 175 shows that the conclusion of the model is insensitive to changes in the input parameters over plausible ranges i.e. TURBT plus a single instillation of chemotherapy remains cost-effective in the all the analyses across all the risk groups.

The variations in the treatment effect duration are perhaps particularly notable as this is one of the uncertainties around the effectiveness of the single instillation of chemotherapy. The analysis shows, unsurprisingly, that the intervention is less cost-effective when the treatment effect duration is decreased. However, crucially, the single instillation of chemotherapy remains cost-effective in all analyses, even when making very pessimistic assumptions about the likely treatment effect duration (i.e. even when assuming that the chemotherapy instillation only reduces recurrences in the first 3 months after administration).

A.4.8 Costing analysis

In addition to the core cost-utility analysis, the GDG were also interested in a cost analysis comparing the cost of delivering the single instillation of chemotherapy on the ward against the cost of delivering it in theatre. Table 176 shows the cost estimations for each approach.

Table 176:Cost comparison of methods for delivering an instillation of intravesical chemotherapy

Therapy	Cost	Source
Ward delivery		
Drug cost		
Mitomycin C (per 40mg vial)	£79.88	British National formulary (BNF)
Delivery cost		
Mito-In system	£4.00	GDG estimate
Advanced nurse consultation	£22.00	Unit costs of health and social care 2012
Additional costs of delivering intravesical chemotherapy (sundries)	£6.50	GDG estimate
Total cost for ward delivery	**£112.38**	
In-theatre delivery		
Drug cost		
Mitomycin C (per 40mg vial)	£79.88	British National formulary (BNF)
Delivery cost		

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Therapy	Cost	Source
Mito-In system	£4.00	GDG estimate
Surgical consultant time (based on GDG estimate of 2 minutes)	£4.67	Unit costs of health and social care 2012
Total cost for ward delivery	**£88.55**	

It can be seen that, according to the cost estimations, delivering the single instillation of chemotherapy in theatre was the cheaper of the two approaches (delivery by nurse estimated to cost an additional £23.83). This was primarily a result of the longer amount of time taken to deliver the instillation in the ward setting compared to in theatre.

A.4.9 Probabilistic sensitivity analysis

The results of 10,000 runs of the probabilistic sensitivity analysis are shown using a cost-effectiveness acceptability curve (CEAC) in figures 41, 42 and 43 for low, intermediate and high risk patients, respectively. The graph shows the probability of each diagnostic strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

It can be seen that at a threshold of £20,000 per QALY, TURBT plus a single instillation of chemotherapy has a very high probability of being cost-effective in the low and intermediate risk groups (100% in both risk groups). However, the probability is substantially lower in high risk patients at 66%, although still substantially in favour of TURBT plus a single instillation of chemotherapy.

Figure 41: Cost-effectiveness acceptability curves for low risk patients

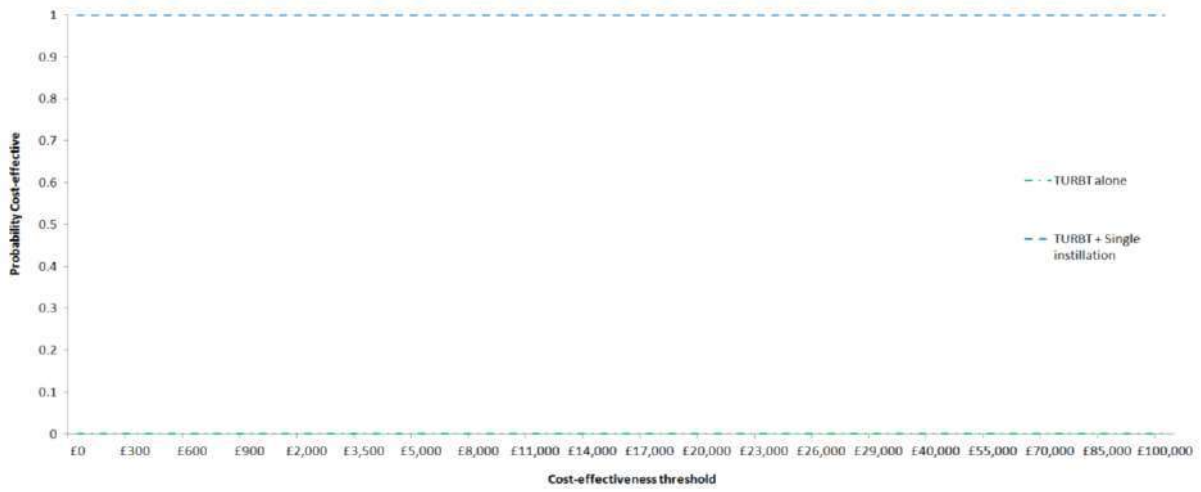

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Figure 42: Cost-effectiveness acceptability curves for intermediate risk patients

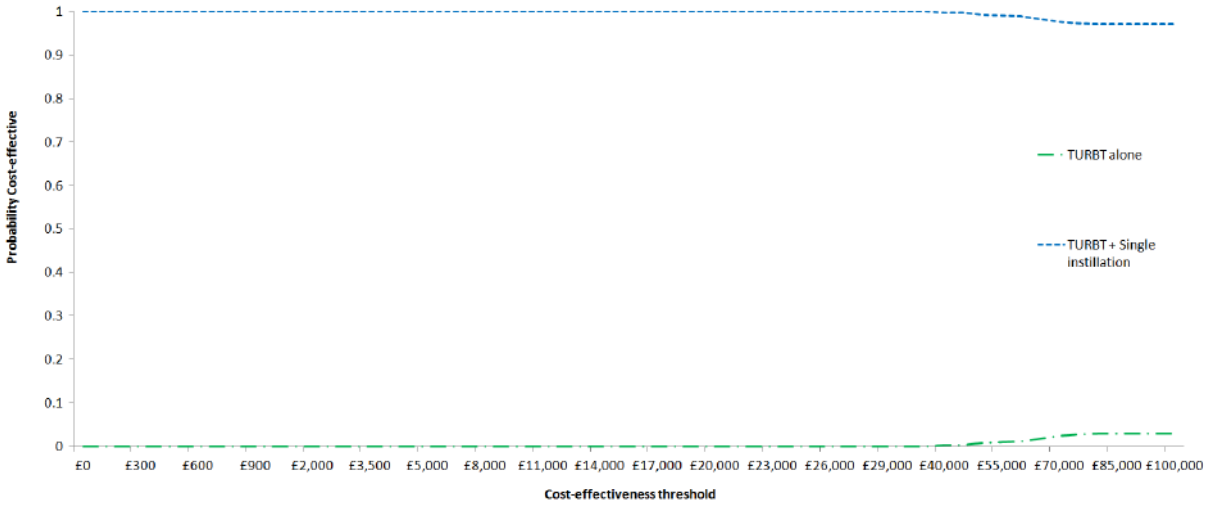
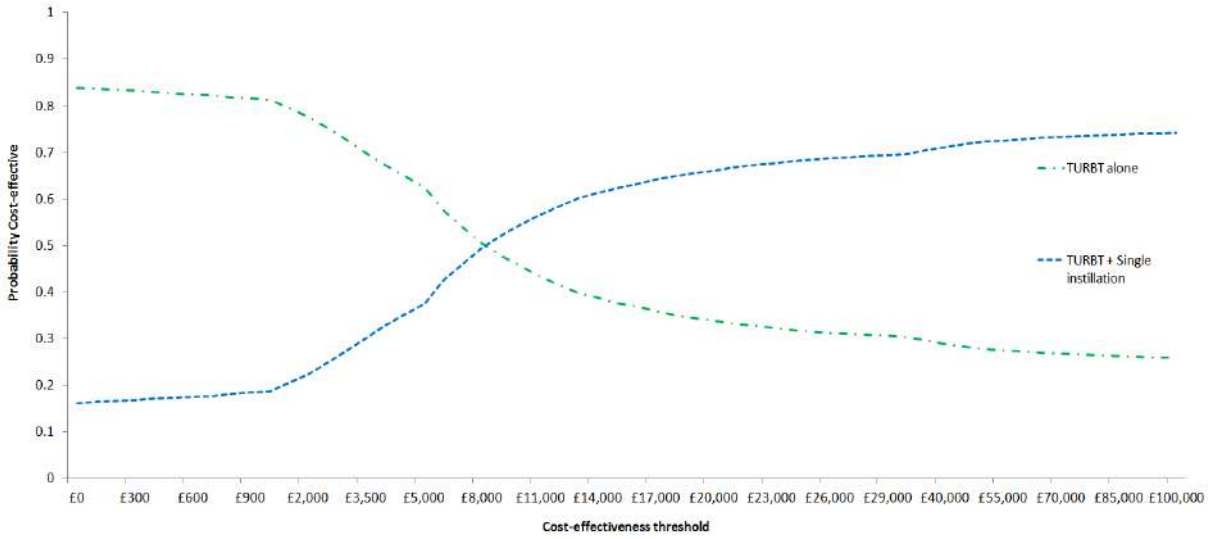


Figure 43: Cost-effectiveness acceptability curves for high risk patients



A.4.10 Discussion

This analysis aimed to estimate the cost-effectiveness of administering a single instillation of intravesical chemotherapy immediately after a TURBT in comparison to a TURBT alone. The base case results of the model suggest that a single instillation immediately after a TURBT is a cost-effective strategy in low, intermediate and high risk patients with NMIBC.

The strategy was shown to be particularly cost-effective in low and intermediate risk patients where the cost savings driven by the reduction in recurrences were large enough to offset the initial higher costs associated with administering the chemotherapy. Thus, in low and intermediate risk groups, the administration of a single instillation of chemotherapy after a TURBT was shown to be cheaper and more effective and was thus considered dominant.

In high risk patients, cost savings from reduced recurrences are not large enough to completely offset the initial costs of administering the chemotherapy (i.e. not cost saving). However, while the strategy was more expensive, the QALY benefits obtained are substantial enough to make the single instillation of chemotherapy cost-effective. The base case estimate suggests that, in high risk patients, a single instillation of chemotherapy after

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TURBT provides one additional QALY at a cost of £6,432, which is well below the NICE threshold of £20,000 per QALY.

Furthermore, the results of the one-way sensitivity analysis suggested that the base case results were robust with the conclusion of the analysis remaining unchanged in all of the low, intermediate and high risk group analyses. Moreover, the probabilistic sensitivity analysis showed that, at a threshold of £20,000 per QALY, the probability of a TURBT plus a single instillation of chemotherapy being cost-effective in comparison to TURBT alone was high in all risk groups (100%, 100% and 66% in the low, intermediate and high risk groups, respectively).

However, it should be noted that there are numerous limitations to the analysis. As with most economic analyses, the analysis is highly dependent upon the clinical data upon which it is based. In this instance, the evidence for a reduction in the risk of recurrence is actually of high quality with numerous well conducted studies observing the effect. However, there are uncertainties elsewhere that have necessitated assumptions in the model.

The duration of the treatment effect is one such uncertainty. In the base case analysis it was assumed that the treatment effect (i.e. reduction in recurrence risk) would apply for two years after the administration of the chemotherapy (assuming that there are no recurrences during the 2 year period). This reflects the general consensus around the possible treatment effect duration but it's possible that it may be lower. However, the influence of the treatment effect duration was explored in sensitivity analysis and it was found that, while it is influential, the conclusions of the base case analysis were unchanged even in the most pessimistic scenario.

There was also found to be a paucity of quality of life data in this area. This is a common issue in cost-effectiveness evaluations but is nevertheless a significant one. The QoL values applied in the model are all of generally low quality and so the estimated QALYs may not be robustly estimated. However, the model is primarily driven by costs and the influence of this QoL values is likely to be limited.

A.4.11 Conclusion

The results of the analysis suggest that the use of a single instillation of chemotherapy after a TURBT, in comparison to a TURBT alone, was found to be strongly cost-effective in all risk groups. It was found to be particularly cost-effective in low and intermediate risk groups, in which the strategy was cost saving as well as more effective (dominant). Furthermore, this result was found to be robust in alternative scenario analyses, one-way and probabilistic sensitivity analysis.

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Appendix B: The cost-effectiveness of reduced follow-up and/or follow-up using newer tests and techniques in comparison to the test and protocols used in current practice in non-muscle-invasive bladder cancer patients

B.1 Background

There is general agreement that patients with non-muscle invasive bladder cancer (NMIBC) require regular cystoscopic surveillance of their bladder to check for recurrence. However, there is no agreement upon the optimal frequency and length of cystoscopic follow-up and, as such, there is significant variation in clinical practice.

Many advocate tailoring follow-up strategies to patients in the different NMIBC risk groups (low, intermediate and high). This could allow for follow-up to be safely reduced in the lower risk groups whilst ensuring that the higher risk patients are still monitored closely.

In addition, the use of alternative tests to cystoscopy, such as urinary biomarkers and cytology, could have a useful role in reducing the burden of cystocopies. However, the effectiveness and cost-effectiveness of such approaches has never been reliably demonstrated.

B.2 Aims

To estimate the cost-effectiveness of reduced follow-up and/or follow-up using newer tests and techniques in comparison to the test and protocols used in current practice in NMIBC patients.

B.3 Existing Economic Evidence

A systematic literature review was performed to assess the current economic literature in this area. The review identified 515 possibly relevant economic papers relating to bladder cancer. Of these, 50 full papers were obtained for appraisal. However, none of the papers included a cost-utility analysis that addressed the decision problem at hand. Despite the absence of cost-utility analyses, three papers were identified that utilised modelling techniques to compare follow-up strategies; De Bekker Grob et al. 2009, Van Kessel et al. 2013 and Zhang et al. 2013.

De Bekker Grob et al. 2009 investigated the cost-effectiveness of a strategy whereby cystoscopy is partly replaced by microsatellite analysis (MA) of urine. The authors constructed a semi-Markov model to investigate two strategies; a conventional strategy consisting of cystoscopy every 3 months and a test arm consisting of MA of voided urine samples every 3 months with a control cystoscopy at 3, 12 and 24 months. The authors found that the probability of being without recurrence after 2 years of surveillance was similar in the two groups (86.6% and 86.3% in the conventional and test arm, respectively). However, the total costs were higher in the test arm (per patient cost of €4,104 versus €3,433 in the conventional arm). Further analysis suggested that the test arm would be as effective and cost the same as the conventional arm if the sensitivity increased to ≥61%, the

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specificity was set to 73% and the costs were decreased from €158 to <€70. The authors concluded that cystoscopy could be partly replaced if the MA urine test had a slightly higher sensitivity and its costs were reduced.

A similar analysis was conducted by Van Kessel et al. 2013, in which the cost-effectiveness of partly replacing cystoscopy with FGFR3 mutation analysis of voided urine samples in Dutch patients with NMIBC was investigated. Three surveillance strategies were compared using a Markov model; standard surveillance defined as cystoscopy every three months, minimal surveillance defined as cystoscopy at 3, 12 and 24 months and modified surveillance consisting of FGFR3 mutation analysis of voided urine samples every 3 months and cystoscopy at 3, 12 and 24 months. The analysis was stratified for three risk profiles, including surveillance after 1) the primary tumour, 2) the first to third recurrence and 3) the fourth recurrence or more. The authors found that the probability of no recurrence after two years of surveillance was higher for the modified surveillance than the standard or minimal surveillance arms, e.g. after primary tumours (95.7%, 95.0% and 93.9%, respectively). The total cost of surveillance after the primary tumour was lower for minimal and modified surveillance (€2,254 and €2,558, respectively) than for standard surveillance (€5,861). The results were consistent in all three risk profiles and were robust to changing inputs over plausible ranges. The authors concluded that surveillance in which cystoscopy is partly replaced by FGFR3 mutation analysis of urine seems a safe, effective and cost-effective surveillance strategy.

The analysis conducted by Zhang et al. 2013 compared surveillance strategies for low risk non-muscle invasive bladder cancer patients. The study was not a cost-effectiveness analysis and indeed did not even consider costs but it did estimate QALYs for each strategy. The authors developed a Markov model to compare surveillance strategies recommended in international guidelines and additional proposed strategies. The authors found that age and co-morbidities significantly affect the optimal surveillance strategy. The results suggested that younger patients should be screened more intensively than older patients and patients with co-morbidities should be screened less intensively.

B.4 De Novo Economic Model

Since the current economic literature didn't adequately address the decision problem[n], a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel. The basic model structure is shown in Figure 44.

Figure 44: Basic model structure

n It should be noted that, while none of the above studies met the requirements for inclusion in the systematic review, they were nonetheless informative in helping to develop our own de novo economic model.

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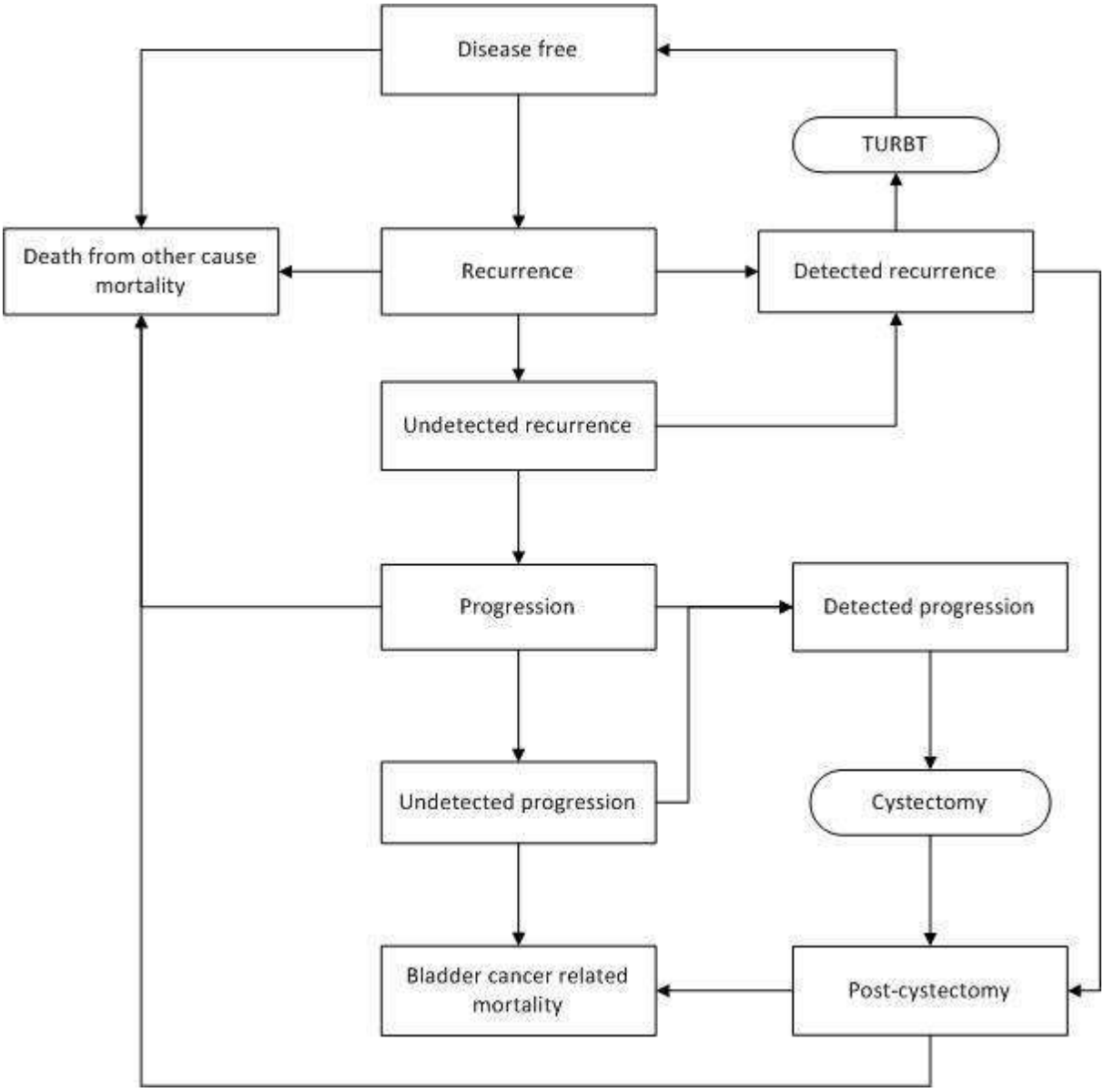

The patient enters the model in a 'disease free' state following an initial transurethral resection of the bladder tumour (TURBT). At each 3-monthly model cycle the patient may experience a bladder cancer recurrence. If the recurrence is detected, the patient will undergo a further TURBT (or fulguration of the tumour) and return to a disease free state. However, if the recurrence is not detected, then the patient will be at risk of progression and will have to undergo further treatment once this progression is eventually detected (cystectomy and possibly neo-adjuvant chemotherapy). The patient may also die from bladder cancer related mortality after experiencing progression and may die from other cause mortality from any health state.

Estimated total costs and quality adjusted life years (QALYs) are collected over the modelled 10 year time horizon for each follow-up strategy. The total costs will include all costs associated with surveillance, treatment and management and are described in more detail in the cost section of this report. QALYs are calculated by multiplying the life years that patients spend in each health state by the associated quality of life (QoL) weighting, which represent the patient's valuation of their health state. QALYs and QoL values are discussed in more detail in later sections of the report.

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Future costs and benefits were discounted at a rate of 3.5% per year as recommended by NICE.

B.4.1 Natural history of disease - risk of recurrence and progression

The risk of recurrence and progression in patients with NMIBC was estimated using risk equations based on an analysis of 2,596 patients from seven EORTC[o] trials (Sylvester et al. 2006). Patients are 'scored' based on a number of risk factors, such as number of tumours, tumour size, prior recurrence rate, T category, presence of CIS and grade. The scores associated with the risk factors are shown in Table 177 below.

Table 177: EORTC scores associated with risk factors

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2 to 7	3	3
≥ 8	6	3
Tumour size		
< 3cm	0	0
≥ 3cm	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 rec/yr	2	2
> 1 rec/yr	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total risk score	0-17	0-23

The overall recurrence and progression risk scores computed from the above table have an associated one year and five year risk of recurrence and progression. The one year and five year risks of recurrence and progression are shown in Tables 178 and 179.

Table 178: EORTC recurrence probabilities for recurrence score groups

Recurrence score	1 year probability of recurrence	5 year probability of recurrence
0	**15.0%** (10%, 19%)	**31.0%** (24%, 37%)
1 - 4	**24.0%** (21%, 26%)	**46.0%** (42%, 49%)
5 – 9	**38.0%** (35%, 41%)	**62.0%** (58%, 65%)
10 – 17	**61.0%** (55%, 67%)	**78.0%** (73%, 84%)

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Table 179: EORTC progression probabilities for progression score groups

Progression score	1 year probability of progression	5 year probability of progression
0	**0.2%** (0%, 0.7%)	**0.8%** (0%, 1.7%)
2 – 6	**1.0%** (0.4%, 1.6%)	**6.0%** (5%, 8%)
7 – 13	**5.0%** (4%, 7%)	**17.0%** (14%, 20%)
14 – 23	**17.0%** (10%, 24%)	**45.0%** (35%, 55%)

For the purposes of the economic model, it was necessary to convert these five year and one year risks into 3-monthly risks to match the model cycle length used. In order to capture the higher risk of recurrence and progression in the first year, separate 3 monthly risks were used in the first year and in subsequent years (based on the one year risk and five year risk, respectively).

Furthermore, since the EORTC risk equations consider recurrence and progression independently, it was necessary to link the progression rates to the recurrence rate i.e. estimate the probability of progression given recurrence in each of the risk groups. Note that had this approach not been adopted then the benefit of follow-up would be negligible as there would be no benefit associated with detecting recurrences earlier.

Note that the risk group classifications used in clinical practice do not translate neatly to any one set of recurrence and progression risk. There are multiple permutations of recurrence and progression risk that are possible in each of the clinical risk groups as shown in Table 180.

Table 180: Recurrence and progression risk scores for each risk group variant

Clinical risk group	Recurrence score	Progression score	Example
Low risk			
Base case values	0	0	Solitary tumour, <3cm, Ta, G1
Variant 1	1-4	0	Solitary tumour, <3cm, Ta, G2
Intermediate risk			
Base case values	1-4	2-6	Solitary tumour, >3cm, Ta, G1
Variant 1	5-9	2-6	2-7 tumours, >3cm, Ta, G1
Variant 2	10-17	7-13	>8 tumours, >3cm, T1, G1
High risk			
Base case values	10-17	14-23	>8 tumours, >3cm, T1, G3
Variant 1	5-9	7-13	Solitary tumour, >3cm, Ta, G3
Variant 2	5-9	14-23	2-7 tumours, >3cm, T1, G3
Variant 3	10-17	7-13	>8 tumours, >3cm, T1, G2

In the base case analysis, the recurrence and progression risk combinations that are likely to best reflect the majority of patients within each clinical risk group were selected. Variations in the recurrence and progression score are assessed in sensitivity analysis. Table 181 shows the three monthly risks of recurrence, progression and progression given recurrence applied for each of the risk groups in the base case analysis.

Table 181: Three monthly recurrence and progression risk applied in the model

Outcome	3 monthly rates		
	Recurrence	Progression given recurrence	Progression

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First year			
Low risk	3.98%	1.26%	0.05%
Intermediate risk	6.63%	3.78%	0.25%
High risk – Lower	11.26%	11.31%	1.27%
High risk – Upper	20.97%	21.70%	4.55%
Subsequent years			
Low risk	1.84%*	2.18%*	0.04%*
Intermediate risk	3.03%	10.18%	0.31%
High risk – lower	4.72%	19.64%	0.93%
High risk – upper	7.29%	40.39%	2.94%

Note that since the modelled time horizon of 10 years exceeds the predicted risk estimates from the EORTC trials (5 years), it was also necessary to make some assumptions about the risk profile of patients in years 5-10. In the base case, it was assumed that the estimated subsequent year rate (i.e. years 2-5) would be maintained in years 6-10 except in the case of low-risk patients in whom it was assumed that risk would be zero after 5 years (reflecting the clinical practice of discharging low-risk patients from follow-up protocols after 5 years).

It should also be noted that, in accordance with the EORTC risk scores, modelled low risk and intermediate risk patients that experience a recurrence will thereafter be subject to the higher risk of recurrence and progression associated with the risk level above. For example, low risk patients that have a recurrence are thereafter subject to the recurrence and progression risk scores associated with intermediate risk patients. However, there are nuances to this increased risk which cannot be accurately captured in the model as it does not model changes in tumour characteristics directly. For example, it is not always the case that a recurrence would place an intermediate risk patient into a higher risk group as it would depend on the patient's initial score.

B.4.2 Follow-up strategies

The follow-up strategies considered in the model are summarised below.

B.4.2.1 Current practice

There is variation in current practice and the strategy most commonly used is not definitively known. The GDG adjudged that the strategies described by Hall et al. 1994 best reflect current practice and so these were used in the analysis. The strategies are summarised in Table 182 each risk group:

Table 182: Current practice follow-up strategies

Risk group	Follow-up strategy
Low risk	Cystoscopy at 3 months, 1 year and annually thereafter
Intermediate risk	Cystoscopy every 3 months for 2 years, then every 6 months for 2 years and annually thereafter
High risk	Cystoscopy every 3 months for 2 years, then every 6 months for 2 years and annually thereafter

B.4.2.2 Variations in follow-up frequency

The GDG were interested in follow-up strategies with reduced frequency across each of the risk groups. Two strategies were evaluated in each risk group; a 'slightly reduced frequency follow-up strategy' and a 'reduced frequency follow-up strategy'. The reduced frequency strategies are shown in Table 183 and 184.

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Table 183: Slightly reduced frequency follow-up strategies

Risk group	Follow-up strategy
Low risk	Cystoscopy at 3 months and annually thereafter
Intermediate risk	Cystoscopy every 3 months for 1 year, then 6 monthly for 2 years and annually thereafter
High risk	Cystoscopy every 3 months for 2 years and annually thereafter

Table 184: Reduced frequency follow-up strategies

Risk group	Follow-up strategy
Low risk	Cystoscopy at 3 months, 1 year and then discharge
Intermediate risk	Escalating intervals up to 1 year, with cystoscopy at 3 months, 9 months, 18 months, 30 months and annually thereafter.
High risk	Cystoscopy every 3 months for 1 year, then 6 monthly for 1 year and annually thereafter

Note that those patients found to have a recurrence would have their recurrence treated with a TURBT. Following the TURBT, the patient would then be followed-up in the same manner as after the initial recurrence (i.e. 'resetting the clock') except in the case of low risk patients where the schedule is assumed to be adjusted to reflect the patient's higher risk and thus they are moved to the schedule used in intermediate risk patients.

To assist clarity in the decision analysis[p], it is assumed that when low risk patients change to the intermediate schedule they always receive conventional follow-up regardless of their initial follow-up. For example, a low risk patient receiving the reduced follow-up schedule that has a recurrence would move onto the intermediate schedule used in current practice.

B.4.2.3 Variations in follow-up test

In addition to variations in the frequency of follow-up, the GDG were also interested in the use of a urinary biomarker (FISH) or cytology. In particular, the GDG were interested in combinations of reduced follow-up strategies with FISH or cytology used as a safety net to detect recurrences at the time points that would normally be checked under current practice. Table 185 shows an example of the 'safety net' strategy for a section of time points in the high risk group.

Table 185: Variations in follow-up test example

Diagnostic test	15 months	18 months	21 months	24 months	27 months
Current practice	Check	Check	Check	Check	No check
Reduced follow-up - cystoscopy	No check	Check	No check	Check	No check
Reduced follow-up - FISH	Check	No check	Check	No check	No check

B.4.3 Clinical effectiveness data

B.4.3.1 Diagnostic accuracy data

The diagnostic accuracy data applied in the model (sensitivity and specificity) are shown in Table 186. The data were sourced from the systematic review of the clinical evidence

p If this strategy was not adopted then it would not be clear what change was affecting the overall results e.g. reduced follow-up in low risk patients may appear cost-effective but the result may be driven by reduced follow-up in intermediate patients.

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conducted for this guideline, with most data being sourced from a systematic review by Mowatt et al. 2010. It can be seen that, according to the evidence review, FISH is likely to detect the most cancers (i.e. highest sensitivity) while cytology will produce the least false positives (i.e. highest specificity).

Table 186: Diagnostic accuracy of follow-up tests

Diagnostic test	Value	PSA distribution	Source
Sensitivity			
Flexible cystoscopy	71%	Beta (alpha = 71, beta = 29)	Systematic review
Cytology	46%	Beta (alpha = 46, beta = 54)	Systematic review
FISH	72%	Beta (alpha = 72, beta = 28)	Systematic review
Specificity			
Flexible cystoscopy	72%	Beta (alpha = 72, beta = 28)	Systematic review
Cytology	95%	Beta (alpha = 95, beta = 5)	Systematic review
FISH	86%	Beta (alpha = 86, beta = 14)	Systematic review

B.4.3.2 Bladder cancer related mortality

Bladder cancer related mortality rates were estimated using data identified in the systematic review of the clinical evidence. A systematic review by Van den Bosch et al. 2011 was utilised, which estimated survival rates in high risk NMIBC patients that have progressed to MIBC. In the report, the assumption was made that patient that die from bladder cancer must first progress to muscle invasive disease and then to metastatic cancer. The same assumption was made in the economic model.

Van den Bosch et al. 2011 reported a disease specific survival rate of 35% in NMIBC patients that have undergone a cystectomy and experienced progression over a median follow-up time of 48-123 months. This was converted to an estimated 3 monthly disease specific mortality rate of 3.6% in patients that have progressed to MIBC in the model. In NMIBC patients, the estimated disease specific mortality rate applied in the model was 0.5%. This lower rate reflects that patients would have to first progress to MIBC before dying of bladder cancer (based on the 21.3% progression rate reported in Van den Bosch et al. 2011).

Note that, by using these mortality rates, the model distinguishes between patients that have NMIBC and patients that have progressed to MIBC at the time of cystectomy. This therefore represents one of the benefits of follow-up with patients followed-up more frequently or intensively being less likely to progress to MIBC and therefore will not be subject to the higher mortality rate in this group.

It should also be noted that patients with undetected progression are assumed to be subject to the mortality rate associated with MIBC.

B.4.3.3 Other cause mortality

Death from other causes was captured using 2009-2011 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. In the base case, the model was run

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with an average age of 60 and was assumed to be 50% female (note that these parameters only influence other cause mortality in the model). The annual probabilities of other mortality were converted to three-monthly probabilities for use in the model.

B.4.4 Cost data

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. GP visit). Where possible, all costs were estimated in 2012-13 prices.

The majority of costs were sourced from NHS reference costs 2012/13 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dosages from the British National Formulary (BNF) and unit cost information from the electronic market information tool (eMit). Where unit costs for drugs were not available from eMit, prices from the BNF were used.,Resource use and cost information were obtained from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

Costs for each aspect of the treatment pathway are detailed in the relevant sections below.

B.4.4.1 Follow-up costs

Post resection follow-up

The costs associated with the tests used in the various post-resection follow-up strategies are shown in Table 187.

Table 187: Diagnostic follow-up test costs

Diagnostic test	Cost	PSA distribution	Source
Flexible cystoscopy	£401.88	Gamma (SE = 158.85, alpha = 6, beta = 63)	NHS ref costs 12-13
Cytology	£114.55	Gamma (SE = 84.91, alpha = 2, beta = 63)	Rodger et al. 2006 (inflated to 2012 price)
FISH	£185.10	Gamma (SE = 137.21, alpha = 2, beta = 102)	Ashish Chandra and Michael Neat personal correspondence

The cost of a flexible cystoscopy applied in the model was £401.88, which was based upon the cost of a “Diagnostic Flexible Cystoscopy, 19 years and over” as a day case procedure from NHS reference costs. However, there is variation in current practice as to whether cystoscopies are coded as an outpatient or day case procedure. Day case procedures were thought to be more common and thus were selected for the base case analysis but the cost associated with flexible cystoscopies given as outpatient procedures (£164.00) was applied in a sensitivity analysis.

The cost of cytology applied in the model was sourced from a published health technology appraisal (HTA) report by Rodgers et al. 2006, which estimated the cost of cytology to be £92.37 in 2003 prices. This cost was inflated to 2012 prices using the OECD price index and was estimated to be £114.55. However, it should be noted that there is uncertainty over the cost of cytology to the NHS with no robust estimates available. In NHS reference costs, the only cost available for cytology is where it is used as a directly accessed pathology service (£16.92), which is thought to underestimate the likely cost in this context. To reflect the uncertainty around the cost of cytology, it’s cost is varied in sensitivity analysis.

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The urinary biomarker, FISH, is not widely used in current practice and thus sourcing its cost was problematic. In a published HTA report by Mowatt et al. 2010 the cost was estimated to be £54.80. However, the GDG felt that this underestimated the true cost considerably. Thus, the alternative estimate of £185.10 was sourced by a member of the GDG. The estimate incorporated the cost of urovysion analysis, reagents, technical processing and the staff time of two cytopathologists (one to perform analysis and one to check). Alternative costs, including the £54.80 estimated by Mowatt et al. 2010, were explored in sensitivity analyses.

The consequences of inaccuracy in the diagnostic tests should also be noted. True negative and false negative results would only incur the cost of the initial investigation itself whereas true positive and false positive results would incur the cost of the initial investigation and the cost of performing a biopsy ('unnecessarily' in the case of false positive patients, at which point the error would be realised).

B.4.4.2 Recurrence costs

The costs associated with treating recurrences are shown in Table 188.

Table 188: TURBT and diathermy costs used to treat recurrences

Therapy	Proportion	Cost	PSA distribution	Source
TURBT	33%	£1,267.59	Gamma (SE =333.97, alpha = 14, beta = 88)	Estimate from Bill and NHS ref costs 12-13
Diathermy	67%	£401.88	Gamma (SE =158.85, alpha = 6, beta = 63)	Estimate from Bill and NHS ref costs 12-13

Patients that have a recurrence would need further treatment; either another TURBT or diathermy in assumed proportions of 33% and 67%, respectively. The cost of a TURBT was estimated to be £1,267.59, which was based on the cost of an 'Intermediate Endoscopic Bladder Procedure' from NHS reference costs. The cost of diathermy was estimated to be equivalent to the cost of a flexible cystoscopy (£401.88 from NHS reference costs).

B.4.4.3 Further treatment costs

Mitomycin C course

Patients with intermediate risk bladder cancer are assumed to receive a course of Mitomycin C (once weekly for 6 weeks) at a cost of £479.28 (sourced from the BNF). The cost of administering Mitomycin C was obtained from NHS reference costs 2012/13 ('Introduction of Therapeutic Substance into Bladder' – LB17Z). In clinical practice, the therapy is either delivered as an outpatient or day case procedure. Thus, a weighted average cost was calculated based on the number of outpatient and day case admissions listed in NHS reference costs (57% were day case and 43% were outpatient). The average weighted cost of delivering Mitomycin C was estimated to be £220.74 per instillation.

In current clinical practice, some low risk patients may receive a course of Mitomycin c following a recurrence. To capture this in the model it was assumed that 50% of low risk patients would receive a course of Mitomycin C after a recurrence. This assumption was informed by the clinical opinion of the GDG.

Bacillus Calmette-Guérin (BCG) therapy

Patients with high risk bladder cancer and initially low and intermediate risk patients that have had multiple recurrences are assumed to receive Bacillus Calmette-Guérin (BCG)

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therapy. These patients will first receive induction BCG therapy, which consists of six doses of BCG given once a week over a six week period. After a six week off-period, patients that have not had a recurrence or progression will then go onto receive maintenance BCG therapy. This consists of a further three doses given once a week over a three week period at six monthly intervals for a maximum of three years.

Patients that progress to muscle invasive disease while receiving BCG therapy are classed as 'BCG failures' and are assumed to undergo a cystectomy. In addition, in an attempt to reflect the clinical practice of classifying high risk recurrences as BCG failures, it has been assumed that a proportion of recurrences in patients receiving BCG therapy would be BCG failures. In high risk patients it is assumed that 50% of patients with a first recurrence and all patients with two recurrences on BCG therapy would be classed as BCG failures. In low and intermediate risk patients it is assumed that 50% of patients with a first or second recurrence and all patients with three recurrences on BCG therapy would be classed as BCG failures.

The cost of the BCG therapy is based on the average cost of ImmuCyst and OncoTICE with costs sourced from the BNF. The cost of delivering BCG was estimated to be £220.74 and was based on the same NHS reference cost codes used for the MMC course (see above).

The costs associated with bladder instillations (Mitomycin c and BCG) are shown in Table 189.

Table 189: Intravesical instillation costs – Mitomycin C and BCG courses

Therapy	Value	PSA distribution	Source
Bladder instillation costs			
Delivery cost – day case	£285.78	Gamma (SE = 107.66, alpha = 7, beta = 41)	NHS ref costs 12-13 - LB17Z
Delivery cost – outpatient	£133.57	Gamma (SE =46.92, alpha = 8, beta = 16)	NHS ref costs 12-13 - LB17Z
Proportion delivered as day case	57%	Beta (alpha = 57, beta = 43)	NHS ref costs 12-13 - LB17Z
Proportion delivered as outpatient	43%	1 – day case proportion	NHS ref costs 12-13 - LB17Z
Average delivery cost	£220.74	-	-
MMC Course			
Mitomycin C drug costs (once weekly for 6 weeks)	£479.28	Gamma (SE =355.29, alpha = 2, beta = 263)	BNF
Mitomycin C delivery cost	£1,324.42	-	-
BCG therapy			
Induction drug cost (6 doses)	£452.52*	Gamma (SE =335.45, alpha = 2, beta = 249)	BNF
Induction BCG delivery cost	£1,324.42	-	-
Maintenance drug cost (3 doses, every 6 months)	£226.26†	Gamma (SE =167.72,	BNF

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Therapy	Value	PSA distribution	Source
		alpha = 2, beta = 124)	
Maintenance BCG delivery cost	£662.21	-	-

**Based on the average cost of 6 doses of ImmuCyst® (£475.38) and OncoTICE® (£429.66)*
†Based on the average cost of 3 doses of ImmuCyst® (£237.69) and OncoTICE® (£214.83)

Cystectomy and neo-adjuvant chemotherapy

Patients that progress to muscle invasive disease or experience BCG failure are assumed to undergo a cystectomy. The cost associated with a cystectomy was estimated to be £9,538.29 based on the cost of a 'Cystectomy with Urinary Diversion and Reconstruction, with CC Score 0-2' from NHS reference costs.

It was further assumed that 80% of patients undergoing a cystectomy would receive neo-adjuvant chemotherapy. In current clinical practice the majority of patients receiving neoadjuvant chemotherapy receive a regimen of gemcitabine and cisplatin (GemCis) but a minority also receive accelerated MVAC (methotrexate, vinblastine, adriamycin and cisplatin). The proportion of patients receiving each regimen in the model was based on the clinical opinion of the GDG, with 90% receiving GemCis and 10% receiving accelerated MVAC.

Chemotherapy drug costs were estimated using unit costs from the BNF with doses and schedules as recommended by the GDG. Drug doses were estimated using an average body surface area of 1.91m^2 for men and 1.71m^2 for women as reported in a study by Sacco et al. 2010. In addition to the drug costs, the costs associated with delivering chemotherapy were also captured using tariffs from NHS reference costs, which vary depending upon the complexity of delivering the chemotherapy (principally the time required to deliver the chemotherapy). In the case of accelerated MVAC, patients also receive the G-CSF, Pegylated filgrastim at a cost of £686.38 for a 6mg prefilled syringe.

The costs per cycle of chemotherapy are shown in Table 190 for a schedule of GemCis and accelerated MVAC. Patients receiving neoadjuvant chemotherapy are assumed to receive three cycles of chemotherapy as recommended by the GDG.

Table 190: Chemotherapy cost per cycle of GemCis and accelerated MVAC

Therapy	Value	PSA distribution	Source
GemCis			
Proportion of patients receiving GemCis	90%	Beta (alpha = 90, beta = 10)	Assumption
Initial chemotherapy delivery cost*	£267.99	Gamma (SE = 91.36, alpha = 9, beta =31)	NHS reference costs 2012/13 - SB13Z
Deliver subsequent elements of a chemo	£301.56	Gamma (SE = 108.07, alpha = 8, beta = 39)	NHS reference costs 2012/13 - SB15Z
Gemcitabine (1000mg/m2 on days 1,and 8)	£46.02	Gamma (SE = 383.42, alpha = 2, beta = 284)	Unit costs from eMit
Cisplatin (70mg/m2 on day 2)	£21.49	Gamma (SE = 48.16, alpha = 2, beta = 36)	Unit costs from eMit
Total GemCis cost per cycle	£637.05	-	-
Accelerated MVAC			
Proportion of patients receiving MVAC	10%	1 – proportion receiving GemCis	Assumption
Initial chemotherapy delivery cost†	£329.80	Gamma (SE = 146.63, alpha = 5, beta = 65)	NHS reference costs 2012/13 - SB14Z

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Therapy	Value	PSA distribution	Source
Administration of Pegfilgrastim by district nurse*	£35.00	Gamma (SE = 25.95, alpha = 2, beta = 19)	Unit costs of health and social care 2013
Methotrexate (30 mg/m2 given on day 1)	£7.04	Gamma (SE = 27.89, alpha = 2, beta = 21)	Unit costs from eMit
Vinblastine (30 mg/m2 given on day 1)	£6.56	Gamma (SE = 5.27, alpha = 2, beta = 4)	Unit costs from eMit
Adriamycin (30 mg/m2 given on day 1)	£5.28	Gamma (SE = 78.37, alpha = 2, beta = 58)	Unit costs from eMit
Cisplatin (70mg/m2 on day 1)	£21.49	Gamma (SE = 48.16, alpha = 2, beta = 36)	Unit costs from eMit
Pegfilgrastim (6 mg prefilled syringe on day 2 or 3)	£686.38	Gamma (SE = 508.81, alpha = 2, beta = 377)	Unit costs from BNF
Total cost per cycle	£1,091.54	-	-

**Deliver more complex parenteral chemo at 1st attendance†Deliver Complex Chemo, including Prolonged Infusional Treatment, at 1st Attendance*

Post cystectomy follow-up

Patients that have undergone a cystectomy are assumed to be followed up in the manner reflecting current practice with a combination of urological consultations, urethroscopies, CT scans and blood tests (kidney function and PSA). The patient is assumed to be followed up by the urological consultant at three, six and twelve months and annually thereafter at a cost of £94.11 per consultation based on the cost of a 'Non-admitted face to face attendence, follow-up in Urology' from NHS Reference Costs. Urethroscopies are assumed to be used annually at an estimated cost of £672.53, based on the cost associated with a 'Minor or Intermediate Urethra Procedure, 19 years and over' as a day case procedure from NHS Reference Costs. CT scans are assumed to be used on a six monthly basis for the first year and annually thereafter at a cost of £83.85 (NHS Reference Costs). Blood tests are assumed to be done on a six monthly basis at an assumed cost of £20.00. The follow-up costs applied in the model are shown in Table 191.

Table 191: Post-cystectomy follow-up costs

Therapy	Cost	PSA distribution	Source
Urethroscopy	£672.53	Gamma (SE = 214.43, alpha = 10, beta = 68)	NHS ref costs 12-13
CT Scan	£83.85	Gamma (SE = 25.15, alpha = 11, beta = 8)	NHS ref costs 12-13
Blood tests (kidney and PSA tests)	£20.00	Gamma (SE = 14.83, alpha = 2, beta = 11)	GDG assumption
Clinical follow-up (urology consultant)	£94.11	Gamma (SE = 28.41, alpha = 11, beta = 9)	NHS ref costs 12-13

Systemic chemotherapy and palliative care

A metastatic bladder cancer state was not explicitly modelled as such. However, it was assumed that patients that die from bladder cancer related mortality after progressing to muscle invasive disease were likely to have developed metastatic disease. Thus, the costs associated with treating metastatic disease as well as the cost of palliative care were applied to these patients.

It was assumed that the patient would have received systemic chemotherapy, which, as was the case in neoadjuvant chemotherapy, was assumed to be either GemCis or accelerated MVAC in assumed proportions of 90% and 10%, respectively. The chemotherapy doses

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were the same as in the neoadjuvant setting and so the cost per cycle is the same as in the table above for neoadjuvant chemotherapy. However, more cycles of chemotherapy are administered in systemic chemotherapy with patients assumed to receive six cycles of chemotherapy (based on the advice of the GDG).

The cost of palliative care in bladder cancer patients was sourced from a report on deaths from urological cancers in England, 2001-10 by the National End of Life Care Intelligence Network. The palliative care cost was estimated to be £8,502, based on an average length of stay of 11.4 days and an average of 3.1 admissions.

B.4.5 Health-related quality of life data

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs are estimated by combining the life year estimates with utility values (or QOL weights) associated with being in a particular health state. These utility values were identified through a search of the available literature.

There is a paucity of high quality of life (QoL) data available in bladder cancer. In particular, there is a shortage of data on patients with NMIBC with most of the available QoL data focusing on post-cystectomy patients. However, it is recognised that QALYs need to be estimated in order to assess cost-effectiveness using the thresholds employed by NICE (£20,000 - £30,000 per QALY) and thus it is useful to utilise QoL data, even if they are of relatively poor quality. It is however recognised as a limitation of the analysis and the QoL values were subjected to sensitivity analysis to assess how influential they are on the final decision.

For the purposes of this economic evaluation, the QoL data shown in Table 192 were utilised.

Table 192: Health related quality of life weights

Health state	Utilities	PSA distribution	Source
Monitoring	0.780	Beta (alpha = 78, beta = 22)	Mowatt et al. 2010
Post-cystectomy	0.743	Beta (alpha = 74, beta = 26)	Kulkarni et al. 2007
Metastases with systemic chemo	0.600	Beta (alpha = 60, beta = 40)	Kulkarni et al. 2007
Decrements			
TURBT at first recurrence	0.033	Beta (alpha = 3, beta = 97)	SF-36 values from Yoshimura et al. 2005 converted to EQ-5D using mapping algorithm from Ara et al. 2008
TURBT at subsequent recurrence	0.057	Beta (alpha = 6, beta = 94)	
TURBT to detect progression	0.033	Beta (alpha = 3, beta = 97)	

The baseline QoL for patients undergoing monitoring for bladder cancer recurrence (after an initial TURBT) was estimated to be 0.78. This value was sourced from a HTA by Mowatt et al. 2010.

A decrement was utilised for patients that underwent treatment for a bladder cancer recurrence. This was estimated using a study by Yoshimura et al. 2005 that measured QoL in patients with superficial bladder cancer that underwent TURBT. This study measured quality of life using the Short-Form 36-item survey (SF-36), which is not the measure preferred by NICE. Therefore, a mapping algorithm by Ara et al. 2008 was utilised to convert the SF-36 data into EuroQol 5-dimension (EQ-5D) data (the measure preferred by NICE).

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Using this methodology, the QoL decrement for a bladder cancer recurrence was estimated to be 0.033 for a primary recurrence and 0.057 for a subsequent recurrence.

QoL values for patients in a post-cystectomy state and a metastatic state with palliative care (0.743 and 0.600, respectively) were sourced from a health economic study by Kulkarni et al. 2007

B.4.6 Sensitivity analysis

To estimate uncertainty and determine the key drivers of the model, a series of one-way sensitivity analysis were conducted. One-way sensitivity analysis involves changing one input parameter, re-running the model and recording and interpreting the new cost-effectiveness result.

To further estimate uncertainty in the model, probabilistic sensitivity analysis was performed. Probabilistic sensitivity analysis involves running a series of simulations where the values of the model's input parameters are randomly sampled from a distribution around their mean value. This analysis is useful for assessing the uncertainty around all parameter values simultaneously.

The standard errors, distribution type and distribution parameters (alpha and beta values) used to inform the distributions used in the probabilistic sensitivity analysis are shown in each of the input tables in this report. Where possible, the PSA distributions were informed by the standard deviations or standard errors reported in the study or data source. Where data on uncertainty were not available, the distribution parameters were estimated by assuming that the upper and lower quartiles were equal to ±50% of the mean value.

Note that, in general, gamma distributions were used for cost inputs, beta distributions were used for utility values and probabilities, dirichlect distributions were used for conditional variables and normal distributions were used for all other variables.

B.4.7 Results

The results of the economic model are presented as expected costs and QALYs for intervention along with an incremental cost-effectiveness ratio (ICER) for each comparison. The ICER is used to measure the cost-effectiveness of one intervention over another; it is calculated as shown in Figure 45.

Figure 45: Calculation of the incremental cost-effectiveness ratio (ICER)

ICER = (Δ Cost) / (Δ QALYs)

ICER = (Cost Intervention A − Cost Intervention B) / (QALYs Intervention A − QALYs Intervention B)

It can be seen that by dividing the difference in costs of each intervention by the difference in benefits (in QALY terms), a cost per QALY can be calculated for each comparison. NICE typically has a threshold of £20,000 for one additional QALY gained. Thus, an intervention with ICER < £20,000 can usually be considered cost-effective. Interventions with ICER values above £30,000 are not typically considered cost-effective. For ICER values between £20,000 and £30,000, an intervention may be considered cost-effective if it is associated with significant benefits.

The model was run over a time horizon of ten years as this was expected to be the time period over which the outcomes were most likely to differ for patients undergoing each of the follow-up strategies.

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B.4.7.1 Base case results

The base case results of the analysis for are presented in the tables below for patients in each risk category. Table 193 shows the results of each strategy in comparison to current practice ('common baseline' approach) whilst the second table shows the results in 'dominance rank' format as a means to evaluating the best overall strategy.

In the comparisons against current practice, it can be seen that all of the proposed new strategies (reduced frequency or a change in test) would be cheaper than current practice across all the risk groups. However, in effectiveness terms, most of the new strategies are less effective than current practice with the exception of strategies involving FISH in the low and intermediate risk groups. In the case of low and intermediate risk patients, it can be seen that all of the new strategies would be considered cost-effective in comparison to current practice at a threshold of £20,000 per QALY. However, in the case of high risk patients, it can be seen that reduced frequency follow-up strategies or strategies involving cytology were not cost-effective in comparison to current practice, whereas the strategies involving FISH were cost-effective in comparison to current practice.

Table 193: Base case cost-effectiveness results using common baseline (current practice)

Follow-up strategy	Cost		QALYs		Cost per QALY
	Total	Incremental	Total	Incremental	
Low risk					
Current practice	£8,845	-	6.29	-	-
Slightly reduced frequency	£8,675	-£171	6.29	-0.0010	£163,892
Reduced frequency	£4,805	-£4,040	6.26	-0.0381	£106,019
FISH w/ reduced frequency	£8,024	-£822	6.29	0.0002	Dominant
Cytology w/ reduced frequency	£7,206	-£1,639	6.29	-0.0074	£220,092
Intermediate risk					
Current practice	£21,988	-	6.20	-	-
Slightly reduced frequency	£19,970	-£2,071	6.18	-0.0135	£149,597
Reduced frequency	£17,037	-£4,950	6.15	-0.0454	£108,925
FISH w/ slightly reduced frequency	£21,000	-£988	6.20	0.0002	Dominant
FISH w/ reduced frequency	£20,539	-£1,448	6.21	0.0105	Dominant
Cytology w/ slightly reduced frequency	£20,531	-£1,457	6.19	-0.0046	£317,344
Cytology w/ reduced frequency	£18,998	-£2,989	6.19	-0.0034	£873,024
High risk					
Current practice	£27,674	-	5.52	-	-
Slightly reduced frequency	£27,227	-£447	5.47	-0.0471	£9,487
Reduced frequency	£26,637	-£1,038	5.40	-0.1114	£9,316
FISH w/ slightly reduced frequency	£27,459	-£215	5.52	0.0007	Dominant
FISH w/ reduced frequency	£27,112	-£563	5.52	0.0016	Dominant
Cytology w/ slightly reduced frequency	£27,362	-£312	5.50	-0.0168	£18,572
Cytology w/ reduced frequency	£26,903	-£771	5.48	-0.0394	£19,592

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In the dominance rank comparison (Table 194), it can be seen that the optimal strategy in low and intermediate risk patients is the reduced frequency strategy. This strategy is the least effective of all the strategies but the difference is marginal and because it is substantially cheaper than the other strategies it is found to be cost-effective overall.

In the case of high risk groups, it can be seen that the reduced frequency strategy is again the cheapest strategy but it is no longer the preferred strategy in cost-effectiveness terms. Strategies of reduced frequency with a safety net using FISH or cytology were found to be more cost-effective than this strategy with the reduced frequency follow-up strategy with FISH found to be the most cost-effective (more cost-effective than cytology because of the superior sensitivity of FISH in the base case).

Table 194: Base case cost-effectiveness result using dominance rank

Follow-up strategy	Cost		QALYs		Cost per QALY
	Total	Incremental	Total	Incremental	
Low risk					
Reduced frequency	**£4,805**	**-**	**6.26**	**-**	**-**
Cytology w/ reduced frequency	£7,206	£2,401	6.29	0.0307	£78,310
FISH w/ reduced frequency	£8,024	£3,219	6.29	0.0383	£83,990
Slightly reduced frequency	£8,675	£3,869	6.29	0.0371	£104,392
Current practice	£8,845	£4,040	6.29	0.0381	£106,019
Intermediate risk					
Reduced frequency	**£17,037**	**-**	**6.15**	**-**	**-**
Cytology w/ reduced frequency	£18,998	£1,961	6.19	0.0420	£46,660
Slightly reduced frequency	£19,970	£2,933	6.18	0.0320	£91,762
Cytology w/ slightly reduced frequency	£20,531	£3,494	6.21	0.0560	£85,511
FISH w/ reduced frequency	£20,539	£3,502	6.19	0.0409	£62,574
FISH w/ slightly reduced frequency	£21,000	£3,962	6.20	0.0456	£86,845
Current practice	£21,988	£4,950	6.20	0.0454	£108,925
High risk					
Reduced frequency	£26,637	-	5.40	-	-
Cytology w/ reduced frequency	£26,903	£266	5.48	0.0720	£3,698
FISH w/ reduced frequency	**£27,112**	**£209**	**5.52**	**0.0409**	**£5,095**
Slightly reduced frequency	£27,227	£115	5.47	-0.0487	Dominated
Cytology w/ slightly reduced frequency	£27,362	£250	5.50	-0.0184	Dominated
FISH w/ slightly reduced frequency	£27,459	£347	5.52	-0.0009	Dominated
Current practice	£27,674	£563	5.52	-0.0016	Dominated

B.4.7.2 Cystoscopic frequency variations only

The GDG were also interested in an analysis where variations in diagnostic tests were excluded from the analysis with only variations in follow-up frequency considered.

The results of this analysis are shown in Table 195. As in the full analysis, it can be seen that the optimal strategy in low and intermediate risk patients was the reduced frequency strategy. However, in the case of high risk patients, it can be seen that the cystoscopy

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frequency used in current practice was the most cost-effective strategy with a cost per QALY of £9,487 in comparison to the next based strategy (Slightly reduced follow-up).

Table 195: Cost-effectiveness results when only variations in cystoscopy are considered

Follow-up strategy	Cost		QALYs		Cost per QALY
	Total	Incremental	Total	Incremental	
Low risk					
Reduced frequency	**£4,805**	**-**	**6.26**	**-**	**-**
Slightly reduced frequency	£8,675	£3,869	6.29	0.0371	£104,392
Current practice	£8,845	£4,040	6.29	0.0381	£106,019
Intermediate risk					
Reduced frequency	**£17,037**	**-**	**6.15**	**-**	**-**
Slightly reduced frequency	£19,970	£2,933	6.18	0.0320	£91,762
Current practice	£21,988	£4,950	6.20	0.0454	£108,925
High risk					
Reduced frequency	£26,637	-	5.40	-	-
Slightly reduced frequency	£27,227	£590	5.47	0.0642	£9,190
Current practice	**£27,674**	**£447**	**5.52**	**0.0471**	**£9,487**

B.4.7.3 Risk score variants

As mentioned in an earlier section of the report, the EORTC risk equations suggest that multiple permutations of recurrence and progression risk are possible within each clinical risk group. For the base case analysis (above) the recurrence and progression risk combinations that were thought to best reflect the majority of patients were used. Table 196 shows the cost-effectiveness results using alternative combinations of recurrence and progression risk for low, intermediate and high risk patients. The results are presented using the dominance rank format to determine the optimal strategy.

Table 196: Cost-effectiveness results using variants on the clinical risk groups

Follow-up strategy	Cost		QALYs		Cost per QALY
	Total	Incremental	Total	Incremental	
Low risk					
Variant 1 (recurrence score of 1-4 , progression score of 0)					
Reduced frequency	**£6,141**	**-**	**6.25**	**-**	**-**
Cytology w/ reduced frequency	£9,290	£3,150	6.28	0.0261	£120,470
FISH w/ reduced frequency	£10,225	£4,084	6.29	0.0324	£126,014
Slightly reduced frequency	£10,666	£4,526	6.29	0.0315	£143,8638
Current practice	£10,909	£4,768	6.29	0.0322	£147,911
Intermediate risk					
Variant 1 (recurrence score of 5-9, progression score of 2-6)					
Reduced frequency	**£19,518**	**-**	**6.12**	**-**	**-**
Cytology w/reduced frequency	£21,524	£2,006	6.16	0.0415	£48,384
Slightly reduced frequency	£22,600	£3,082	6.15	0.0322	£95,700
FISH w/reduced frequency	£23,045	£3,528	6.17	0.0544	£64,888
Cytology w/slightly reduced frequency	£23,178	£3,661	6.16	0.0410	£89,305
FISH w/slightly reduced frequency	£23,656	£4,138	6.16	0.0457	£90,616

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Follow-up strategy	Cost		QALYs		Cost per QALY
	Total	Incremental	Total	Incremental	
Current practice	£24,647	£5,129	6.16	0.0455	£112,755
Variant 2 (recurrence score of 10-17, progression score of 7-13)					
Reduced frequency	**£21,853**	**-**	**6.00**	**-**	**-**
Cytology w/ reduced frequency	£23,834	£1,981	6.08	0.0803	£24,666
Slightly reduced frequency	£24,923	£3,070	6.07	0.0705	£43,554
FISH w/ reduced frequency	£25,266	£3,413	6.11	0.1048	£32,549
Cytology w/ slightly reduced frequency	£25,482	£3,629	6.09	0.0853	£42,532
FISH w/ slightly reduced frequency	£25,934	£4,081	6.09	0.0931	£43,816
Current practice	£26,830	£4,977	6.09	0.0928	£53,605
High risk					
Variant 1 (recurrence score of 5-9, progression score of 7-13)					
Reduced frequency	£25,041	-	5.75	-	-
Cytology w/ reduced frequency	£25,414	£373	5.80	0.0495	£7,545
FISH w/ reduced frequency	**£25,740**	**£325**	**5.83**	**0.0266**	**£12,205**
Slightly reduced frequency	£25,913	£173	5.79	-0.0391	Dominated
Cytology w/slightly reduced frequency	£26,091	£351	5.81	-0.0144	Dominated
FISH w/slightly reduced frequency	£26,236	£497	5.83	-0.0005	Dominated
Current practice	£26,592	£852	5.83	-0.0010	Dominated
Variant 2 (recurrence score of 5-9, progression score of 14-23)					
Reduced frequency	£25,448	-	5.47	-	-
Cytology w/ reduced frequency	£25,870	£382	5.55	0.0764	£4,955
FISH w/ reduced frequency	**£26,184**	**£314**	**5.59**	**0.0446**	**£7,030**
Slightly reduced frequency	£26,291	£107	5.54	-0.0535	Dominated
Cytology w/slightly reduced frequency	£26,495	£311	5.57	-0.0203	Dominated
FISH w/slightly reduced frequency	£26,650	£46	5.59	-0.0010	Dominated
Current practice	£26,985	£801	5.59	-0.0017	Dominated
Variant 3 (recurrence score of 10-17, progression score of 7-13)					
Reduced frequency	£26,308	-	5.66	-	-
Cytology w/ reduced frequency	£26,571	£243	5.70	0.0366	£7,186
FISH w/ reduced frequency	**£26,793**	**£209**	**5.72**	**0.0191**	**£11,620**
Slightly reduced frequency	£26,944	£166	5.69	-0.0259	Dominated
Cytology w/ slightly reduced frequency	£27,065	£278	5.71	-0.0095	Dominated
FISH w/ slightly reduced frequency	£27,159	£366	5.72	-0.0004	Dominated
Current practice	£27,386	£593	5.72	-0.0007	Dominated

It can be seen that, despite changes in the cost, QALY and ICER values, the conclusions regarding cost-effectiveness are unchanged from the base case analysis. That is, the reduced frequency strategy remains cost-effective in and low and intermediate risk patients while the reduced frequency strategy with FISH remains cost-effective in high risk patients.

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B.4.7.4 One-way sensitivity analysis

The results of the one-way sensitivity analysis are shown in Table 197 for all the modelled risk groups. The optimal strategy, in cost-effectiveness terms, is reported for each of the one-way sensitivity analyses in all of the risk groups in the table below.

Table 197: One-way sensitivity analysis results

	Optimal (most cost-effective) strategy		
Change made	**Low risk**	**Intermediate risk**	**High risk**
Single instillation chemo RR reduction	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
Cost of flexible cystoscopy as an outpatient procedure used (£164.00)	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
100% TURBT to treat recurrences	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
100% diathermy to treat recurrences	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
No TURBT utility decrements	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
No adjuvant chemotherapy	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
100% adjuvant chemotherapy	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
No systemic chemotherapy costs	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
No palliative care costs	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
Palliative care cost for 135 days*	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
Equivalent disease specific mortality rates for MIBC and NMIBC†	Reduced frequency	Reduced frequency	Reduced frequency
Lower FISH cost from Mowatt et al. 2010 (£54.80)	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
Lower cytology cost from NHS reference costs (£16.92)	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
Upper FISH sensitivity (=80%)	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
Lower FISH sensitivity (=62%)	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
Upper FISH specificity (=90%)	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
Lower FISH specificity (=79%)	Reduced frequency	Reduced frequency	FISH w/ reduced frequency
5 year time horizon	Reduced frequency	Reduced frequency	Reduced frequency
Recurrence rate maintained in yrs 6-10	Reduced frequency	n/a	n/a
Recurrence rate set to zero in yrs 6-10	n/a	Reduced frequency	FISH w/ reduced frequency
No symptomatic presentation	Reduced frequency	Reduced frequency	FISH w/ reduced frequency

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**Based upon cost used in a report by the NHS technology adoption centre† The mortality rate form NMIBC is applied to both NMIBC and MIBC patients*

It can be seen that the optimal follow-up strategy in the low and intermediate risk groups remains the same as in the base case in all modelled scenarios i.e. reduced frequency follow-up is always the most cost-effective test.

In the case of the high risk patients, the optimal strategy remains the same as in the base case (i.e. reduced frequency with FISH) in the vast majority of the analyses. However, there are two exceptions where the reduced frequency follow-up becomes the most cost-effective test; one where the modelled time horizon is reduced to five years and another where the bladder cancer specific mortality rates are equivalent for NMIBC and MIBC patients.

GP surveillance scenario

In addition to the comparisons made in the base case analysis, the GDG were also interested in the possibility of using GP surveillance in low risk patients that have been discharged from follow-up as a safety net to pick up possible recurrences. Thus, in the reduced follow-up strategy, it was assumed that patients would visit their GP on an annual basis following discharge from cystoscopic follow-up.

It was assumed that GPs would make the determination of whether the patient has suspected bladder cancer (and thus requires a cystoscopy) based upon the primary symptom of bladder cancer; the presence of haematuria. Table 198 shows the rates of haematuria in patients with and without a bladder cancer recurrence that were applied in the model. These rates were based upon the informed clinical opinion of the GDG with the rates of bladder cancer patients that present with haematuria in initial diagnosis used as a guide. However, it should be noted that these rates are highly speculative and may not reflect the real world situation.

In addition there is also concern that the nuances of haematuria are not captured in the model. Haematuria is likely to present intermittently and so the patient may or may not have haematuria at the time of testing. In addition, the assumed annual visits to the GP is a somewhat artificial construct that is useful for modelling purposes but unlikely to reflect the clinical reality as patents with macroscopic haematuria would be likely to visit their GP as soon as the symptom occurs. However, it was not possible to model this level of detail because of a lack of data on the likely time to develop haematuria following a recurrence.

Table 198: Haematuria in patients with and without a bladder cancer recurrence

	Entering GP surveillance after discharge from follow-up	
Haematuria status	**Patients with recurrence**	**Patients without recurrence**
Macroscopic haematuria	68%	5%
Microscopic haematuria	4%	1%
No haematuria	28%	94%

It was assumed that all patients with macroscopic haematuria would be sent for further cystoscopic investigation. Those patients without macroscopic haematuria were assumed to be tested using a urinary dipstick. If microscopic haematuria was identified then the patient was assumed to be sent for further cystoscopic investigation. The diagnostic accuracy values of the urinary dipstick in detecting haematuria were sourced from a published health technology appraisal (HTA) report (Rodgers et al. 2006). The urinary dipstick's sensitivity was estimated to be 97% while its specificity was estimated to be 75%.

Table 199 shows the cost-effectiveness results in low risk patients with a strategy of reduced follow-up with a GP surveillance safety net included in the decision problem. It can be seen that the GP surveillance strategy does not become the preferred strategy with the reduced frequency follow-up remaining the most cost-effective strategy. However, given the

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reservations around the haematuria inputs stated above, these results can only really be considered speculative and so it is difficult to draw firm conclusions about the potential usefulness of a GP surveillance strategy.

Table 199: Cost-effectiveness results when GP surveillance is included in the decision analysis

Follow-up strategy	Cost		QALYs		Cost per QALY
	Total	Incremental	Total	Incremental	
Low risk					
Reduced frequency	**£4,805**	**-**	**6.26**	**-**	**-**
Cytology w/ reduced frequency	£7,206	£2,401	6.29	0.0307	£78,310
GP surveillance w/reduced frequency	£7,973	£3,168	6.29	0.0342	£92,652
FISH w/ reduced frequency	£8,024	£3,219	6.29	0.0383	£83,990
Slightly reduced frequency	£8,675	£3,869	6.29	0.0371	£104,392
Current practice	£8,845	£4,040	6.29	0.0381	£106,019

B.4.7.5 Probabilistic sensitivity analysis

The results of 10,000 runs of the probabilistic sensitivity analysis are shown using a cost-effectiveness acceptability curve (CEAC) in Figures 46, 47 and 48 for low, intermediate and high risk patients, respectively. The graph shows the probability of each diagnostic strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

In the low and intermediate risk groups, it can be seen from the CEACs that the reduced frequency follow-up strategies initially have the highest probability of being cost-effective at a threshold of zero but this decreases as the threshold increases. At a threshold of £20,000 per QALY, the reduced frequency follow-up strategy has a 98% and 91% probability of being cost-effective in the low and intermediate risk group, respectively.

Figure 46: Cost-effectiveness acceptability curves (CEACs) in low risk patients

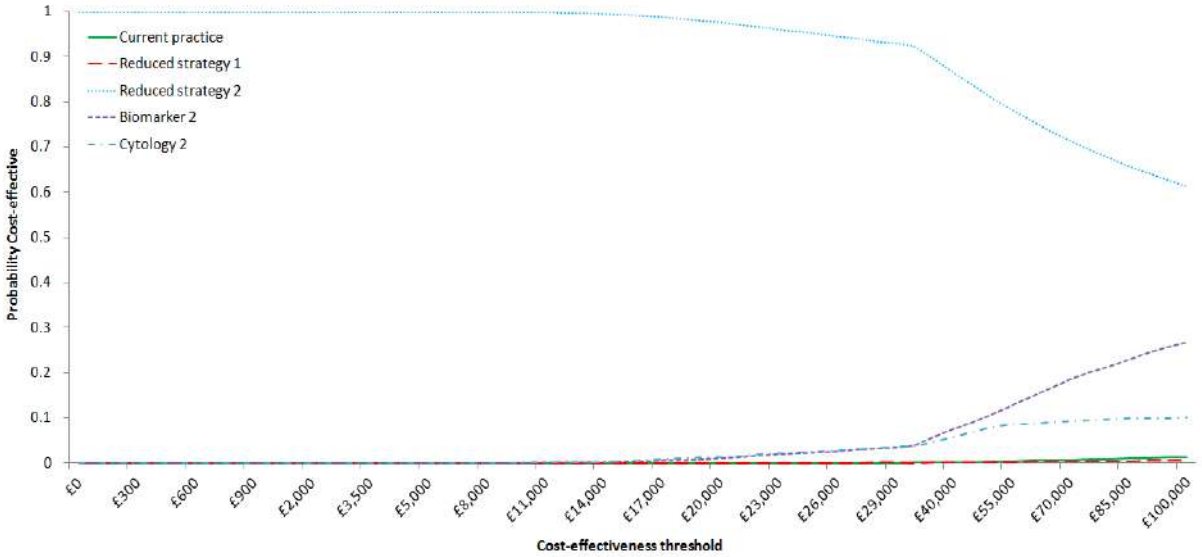


Figure 47: Cost-effectiveness acceptability curves (CEACs) in intermediate risk patients

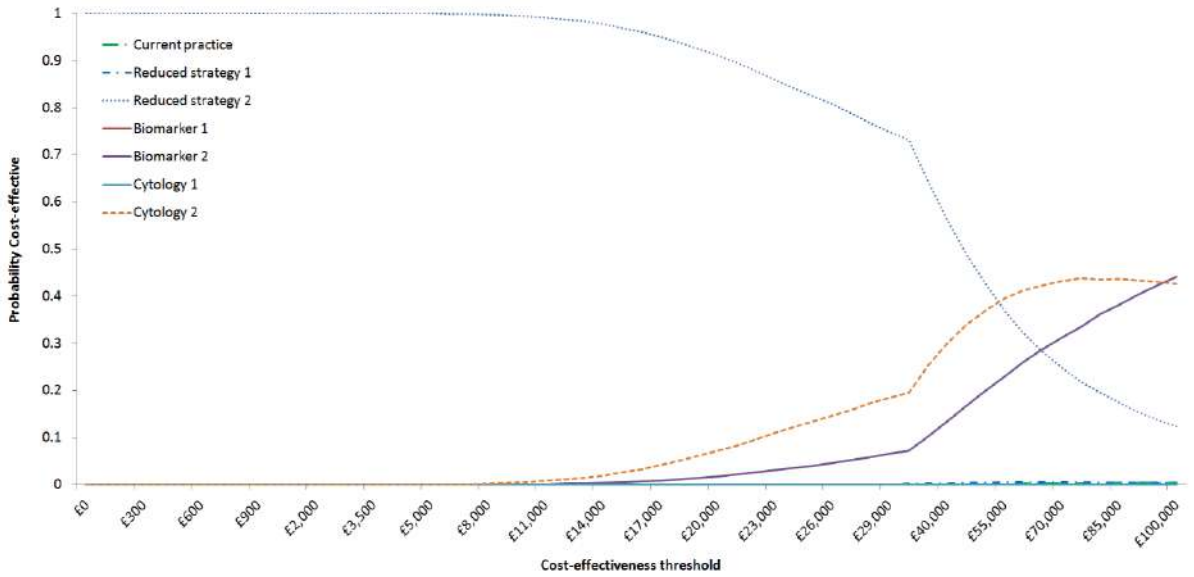
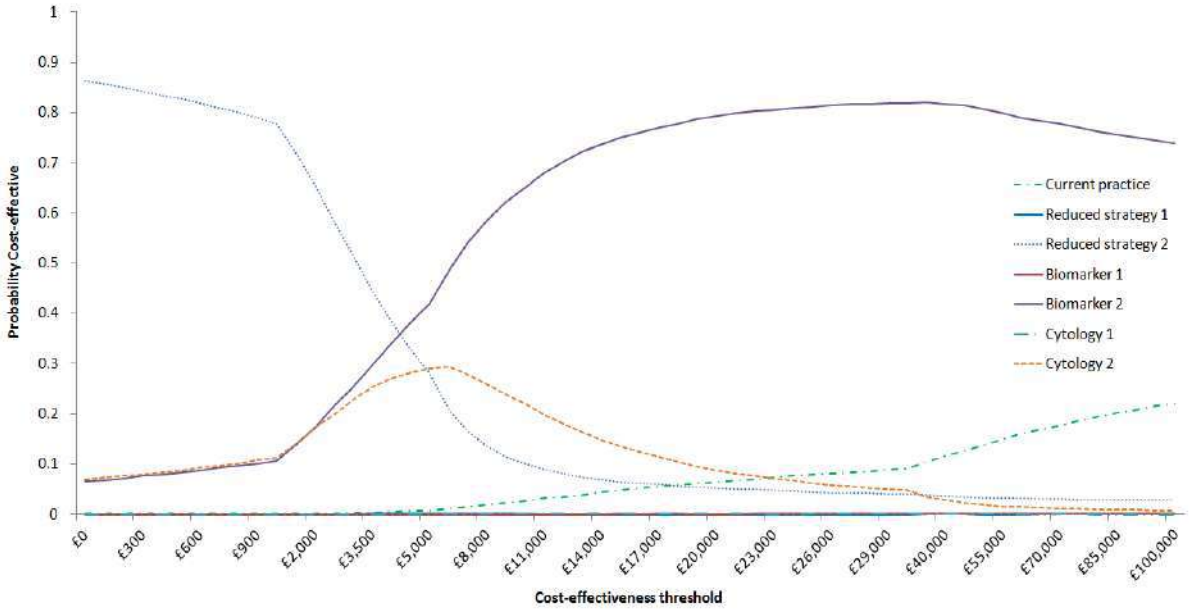


Figure 48: Cost-effectiveness acceptability curves (CEACs) in high risk patients



In the high risk patient group, it can be seen from the CEAC that the reduced frequency follow-up strategy initially has the highest probability of being cost-effective at a threshold of zero but this decreases as the threshold increases. At a threshold of around £4,000 per QALY, the reduced follow-up strategy in combination with FISH becomes the most cost-effective strategy with the probability of it being cost-effective increasing as the threshold increases. At a threshold of £20,000 per QALY, the reduced follow-up strategy in combination with FISH has a 79% probability of being cost-effective.

B.4.8 Discussion

This analysis aimed to estimate the cost-effectiveness of reduced follow-up strategies and/or follow-up using new tests or techniques in comparison to the strategies employed in current

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practice. The base case results of the model suggest that the optimal strategy varies depending upon the patient's clinical risk group. In low risk patients the most cost-effective strategy was found to be a reduced frequency follow-up strategy consisting of cystopscopic follow-up at 3 months, 1 year and then discharge. In intermediate risk patients the most cost-effective strategy was also found to be a reduced frequency follow-up strategy consisting of cystopscopic follow-up at 3 months, 9 months, 18 months, 30 months and annually thereafter. In high risk patients the most cost-effective strategy was found to be a reduced frequency follow-up strategy with FISH used as a safety net. This strategy consisted of cystoscopy every 3 months for 1 year, then every 6 months for 1 year and annually thereafter with FISH used at 15, 21, 30 and 42 months (i.e. the time points that would usually be checked by cystoscopy under current practice follow-up).

A further analysis, in which only variations in follow-up frequency were considered, showed that the most cost-effective test in low and intermediate risk patients remained the same as in the base case analysis i.e. the reduced frequency strategy. However, in the case of high risk patients, the cystoscopy frequency used in current practice was found to be the most cost-effective strategy. This result suggests that it is not cost-effective to reduce the frequency of cystoscopic follow-up in high risk patients without putting a safety net in place in the form of an alternative investigation (such as cytology or FISH).

The results of the one-way sensitivity analysis suggested that the base case results were robust with the conclusion of the analysis remaining unchanged in all of the low and intermediate risk analyses and the vast majority of the analyses conducted in high risk patients.

The probabilistic sensitivity analysis showed that, at a threshold of £20,000 per QALY, the optimal strategy preferred in the base case analyses had high probabilities of being cost-effective. Reduced frequency follow-up has a 98% and 91% probability of being cost-effective in the low and intermediate risk group, respectively while reduced frequency follow-up with FISH has a 79% probability of being cost-effective in high risk patients at a threshold of £20,000 per QALY.

However, it should be noted that there are numerous limitations to the analysis. As with most economic analyses, the analysis is highly dependent upon the clinical data upon which it is based. The systematic review of the clinical evidence for this topic did not reveal any studies comparing the follow-up strategies of interest. Thus, the model was based upon a combination of data sources to attempt to estimate the effectiveness of various follow-up strategies. While every effort has been made to ensure that these data inputs reflect the best available evidence, there is clearly a need for the effectiveness of the follow-up strategies to be compared within clinical trials.

There was also found to be a paucity of quality of life data in this area. This is a common issue in cost-effectiveness evaluations but is nevertheless a significant one. The QoL values applied in the model are all of generally low quality and so the estimated QALYs may not be robustly estimated. However, the model is primarily driven by costs and the influence of this QoL values is likely to be limited.

B.4.9 Conclusion

The results of the analysis suggest that reducing the frequency of cystoscopic follow-up in low and intermediate risk patients is cost-effective. Furthermore, the results show that the addition of cytology or FISH as a safety net was not cost-effective in these risk groups.

In high risk patients, the results of the analysis suggest that reducing cystoscopic follow-up alone is not cost-effective in comparison to current practice. However, the addition of cytology or FISH as a safety net was found to be cost-effective with a reduced frequency follow-up strategy with FISH found to be the most cost-effective strategy.

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However, there are concerns about the lack of comparative data that investigates variations in follow-up and further research is required to fully assess the safety, effectiveness and cost-effectiveness of the proposed follow-up strategies.

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Appendix C: Abbreviations

5-FU	5-Fluorouracil
BCG	Bacillus Calmette-Guerin
CIS	Carcinoma in situ
CNS	Clinical Nurse Specialist
CT	Computed tomography
CTU	Computed tomography urography
EORTC	European organisation for research and treatment of cancer
FDG	Fluorodeoxyglucose
FISH	Fluorescence in situ hybridisation
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
GRADE	Grading of recommendations, assessment, development and evaluation
HDMVAC	High dose methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatin
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
IVU	Intravenous urography
LETR	Linking Evidence to Recommendations
MDT	Multidisciplinary team
MIBC	Muscle invasive bladder cancer
MMC	Mitomycin C
MRI	Magnetic resonance imaging
MVAC	Methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatin
NBI	Narrow-band imaging
NCPES	National Cancer Patient Experience Survey
NMIBC	Non muscle invasive bladder cancer
NMP22	Nuclear matrix protein 22
PCG	Paclitaxel ,cisplatin, gemcitabine
PCN	Percutaneous nephrostomy
PDD	Photodynamic diagnosis
PET	Positron emission tomography
PUNLMP	Papillary urothelial neoplasm of low malignant potential
QALY	Quality adjusted life years
QoL	Quality of Life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
SMDT	Specialist multidisciplinary team
TCC	Transitional cell carcinoma
TUR	Transurethral resection
TURBT	Transurethral resection of bladder tumour
WLC	White light cystoscopy

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Appendix D: Glossary

Adjuvant treatment

A treatment given after the main treatment to reduce the risk of recurrence.

Adverse event

Detrimental change in health occurring in a person receiving the treatment whether or not it has been caused by the treatment.

Antegrade stent

A plastic tube (stent) placed between the kidney and the bladder, within the body's own drainage pipe (the ureter), inserted using access to the kidney, gained through the skin, to relieve a blockage..

Asymptomatic

Without obvious signs or symptoms of disease. Cancer may cause symptoms and warning signs, but, especially in its early stages, cancer may develop and grow without producing any symptoms.

BCG

Originally developed as a vaccine against tuberculosis, BCG is made from modified bacteria from the same family as the tuberculosis bacteria, and is used in the treatment of bladder cancer by instilling it into the bladder through a catheter. It does not contain tuberculosis bacteria and tuberculosis cannot be caught from BCG vaccine.

Biomarkers

Substances found in the blood, other body fluids or tissues. They may be associated with the presence of a certain type of cancer in the body, or may act as a prognostic indicator.

Biopsy

Removal of a sample of tissue from the body to assist in diagnosis or inform the treatment of a disease.

Bladder reconstruction

An operation that reconstructs the bladder using bowel after the bladder has been removed surgically (radical cystectomy).

Bladder substitute (neobladder)

Replacement of the bladder with a reservoir made from bowel, connected to the urethra, to allow urine to be stored and passed in a more or less normal way.

Bone metastases

Cancer that has spread to the bone

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Bone scintigraphy (Isotope bone scan)

A diagnostic imaging technique based on the detection of radiation emitted by a radioactive tracer injected into the body. The tracer is preferentially taken up by bone according to the metabolic activity of the bone and this may help to identify areas of disease, such as cancer.

Cancer networks

Cancer networks became part of Strategic Clinical Networks, serving larger populations, in April 2013.

Carcinoma

A group of cancers which arise from the lining tissues of the body and are the most common type of cancer in humans.

Carcinoma in situ

In the bladder, this means aggressive malignant cells spreading in flat patches within the surface lining (urothelium) of the bladder.

Care plan

A document that details the care and treatment that a person/user receives and identifies who delivers the care and treatment and where this will be delivered.

Chemotherapy

The use of medication (drugs) that is toxic to cancer cells, given with the aim of killing the cells or preventing or slowing their growth.

Clinical effectiveness

The extent to which an intervention produces an overall health benefit in routine clinical practice.

Cohort studies

Research studies in which groups of patients with a particular condition or specific characteristic are compared with matched groups who do not have it.

Comorbidity

The effect of all other diseases an individual person might have other than the primary disease of interest.

Computed tomography (CT)

Imaging technique in which the person lies on a table within a x-ray gantry. The images are acquired using a spiral (helical) path and banks of detectors, allowing presentation of the internal organs and blood vessels in different projections including 3-D views.

Cystoscopy

Examination of the bladder using either a rigid metal or fibreoptic telescope passed into the bladder usually via the urethra (waterpipe).

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Cytology

The microscopic analysis of cells from body fluids or organs, to help to identify and/or assess disease. In the case of urine cytology this refers to the characterisation and enumeration of cells that appear in the urine.

Diagnostic odds ratio (DOR)

The Diagnostic odds ratio (DOR of a test is the ratio of the odds of a positive test in someone with a disease relative to the odds of a positive test in someone without the disease.

Embolisation

An operation done by an X-ray specialist (radiologist) who gains access to the arterial system using a fine plastic tube (catheter) through which material is passed to block the blood supply to an area of tissue. This is usually done to stop bleeding by blocking the blood vessels that supply that tissue that is bleeding.

External beam radiotherapy

This is radiotherapy given by using ionising radiation (e.g. high energy X-rays) produced in a machine and directed at the tumour from outside the person.

False negative

An individual who is truly positive for a disease, but who a diagnostic test classifies as disease-free

False positive

An individual who is truly disease-free, but who a diagnostic test classifies as having the disease

18F-FDG PET CT

A scan that uses a radioactive tracer and combines scanning based on the metabolic activity of a given tissue with CT scan images. It is used to try to identify cancer.

Flexible Cystoscopy

Cystoscopy done using a fibreoptic cystoscope, usually under local anaesthesia.

Fluorescence in situ hybridisation (FISH)

A molecular test that is performed on biopsy or cytology samples. Different molecular labels are applied so that specific genes on the chromosomes show up in different fluorescent colours. The test can be used to show the presence or absence of extra copies of these genes.

Fulguration

Destruction of tissue using diathermy (cautery), generated by passing an electric current through an electrode. Fulguration can be used to destroy bladder cancers, usually at the time of cystoscopy.

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GRADE

The GRADE approach is a method of grading the quality of evidence and strength of recommendations in healthcare guidelines. It is developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.

Grade of cancer

The degree of malignancy of a cancer, judged by its appearance under the microscope. High grade reflects a more aggressive-looking cancer than low grade.

Gy (Gray)

Unit of radiotherapy dose

Haematuria

The presence of blood in the urine. It can be visible, or only detectable by urine testing (non-visible haematuria), depending on the amount of blood in the urine.

Heterogeneity

A term used to describe the amount of difference between results or effects.

High risk non muscle invasive bladder cancer

Cancer in the surface lining (urothelium) or connective tissue layer (lamina propria) of the bladder, deemed to be at high risk of subsequent spread into or beyond the muscle wall of the bladder.

Histopathology

Examination of tissue using a microscope

Holistic needs assessment

An individualised package of information and support for people with cancer and, if they wish, their partners, families or carers.

ImmunoCyt™

A trade name applied to a specific test that can be applied to urine samples to try to label and identify cancer cells.

Immunotherapy

The use of medication or vaccines to manipulate a person's immune system to fight disease.

Incidence

The number of new cases of a disease in a given time period

Incremental cost-effectiveness ratio (ICER)

The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.

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Information prescriptions

These provide up-to-date and accurate information from the NHS and from patient organisations about a persons condition and treatment options; local care services (ranging from the local GP surgery, to equipment to help you get around the house, to specialised exercise classes); benefits a person may be able to claim; housing support; self help and support groups. Information prescriptions also provide useful contact details and website addresses.

Intermediate risk non muscle invasive bladder cancer

Cancer in the surface lining (urothelium) or connective tissue layer (lamina propria) of the bladder, deemed to be at moderate risk of subsequent spread into or beyond the muscle wall of the bladder.

Intractable bleeding

Bleeding which cannot be stopped by conventional means.

Intravesical therapy

Treatment given into the bladder by instillation through a catheter.

IVU

A type of X-ray that uses an injected intravenous contrast agent that is excreted by the kidneys into the urine, thus outlining the kidneys, ureters and bladder when X-rays images are taken.

Lamina propria

The connective tissue layer of bladder. It lies between the lining of the bladder (urothelium) and the main muscle wall of the bladder (detrusor muscle).

Lead time bias

A bias seen in epidemiology studies of survival resulting from differences in the time point at which the disease is first diagnosed which leads to an apparent improvement in survival of the group detected earlier.

Local recurrence

The reappearance of cancer cells after treatment, close to where the cancer was originally found, as opposed to spread to elsewhere in the body (metastasis). In bladder cancer, if cancer comes back anywhere within the bladder, this is regarded as recurrence.

Locally advanced bladder cancer

Bladder cancer that has started to invade into the surrounding structures and / or the lymph nodes in the pelvis or beyond.

Low risk non muscle invasive bladder cancer

Cancer in the surface lining (urothelium) or connective tissue layer (lamina propria) of the bladder, deemed to be at low risk of subsequent spread into or beyond the muscle wall of the bladder.

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Lymphovascular invasion

Cancer cells invading blood and lymph vessels.

Lymph nodes

Small structures which act as filters in the lymphatic system, and in which cells of the immune system are found. Lymph nodes close to the primary tumour are often the first sites to which cancer spreads.

Malignant

A tumour that can invade and destroy nearby tissue and spread to other parts of the body, eg a cancer, a lymphoma or a sarcoma.

Magnetic resonance imaging (MRI)

A type of scan which uses a magnetic field and radio waves to produce images of sections of the body.

Meta-analysis

A form of statistical analysis used to synthesise results from a collection of individual studies.

Metastases/metastatic disease

Spread of cancer away from where it started (the primary site) to somewhere else via the bloodstream or the lymphatic system.

Spread of cancer away from the primary site to somewhere else via the bloodstream or the lymphatic system.

Mitomycin C

A chemotherapy drug that can be used intravenously to treat cancer. It has also been widely used by instillation into the bladder to treat bladder cancer (intravesical therapy).

Morbidity

Detrimental effects on health.

Mortality

Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in relation to any specific region, age group, disease, treatment or other classification, usually expressed as deaths per 100, 1,000, 10,000 or 100,000.

Multi Disciplinary Team (MDT)

A team with members from different health care professions and specialties (e.g. urology, oncology, pathology, radiology, nursing).

Multi Disciplinary Team Meeting (MDTM)

A meeting where members of the Multi Disciplinary Team discuss and make recommendations about the care of people.

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Muscle invasive bladder cancer (MIBC)

Cancer that involves the muscle of the bladder wall.

Narrow band imaging (NBI)

A technology used to try to improve the chance of identifying cancer during cystoscopy. It involves the use of restricted wavelengths of light, rather than white light.

National cancer patient experience survey

A survey done to gather information about the experiences of people with cancer in their dealings with the NHS

Neoadjuvant

Treatment given before the main treatment.

Nephrostomy

A tube used to drain the kidney, usually because of obstruction to drainage either within or close to the urinary tract, eg cancer, stone, the effect of other treatment. It is placed through the skin of the loin directly into the kidney, usually under local anaesthetic by a doctor using X-rays or a scan to aid them.

Nomograms

A calculation aid based on statistical probabilities, which is used to provide individualised estimates of the likelihood of clinical outcomes.

Non muscle invasive bladder cancer (NMIBC)

Cancer in the surface lining (urothelium) or connective tissue layer (lamina propria) of the bladder, rather than cancer that involves the muscle wall of the bladder.

Oncology

The study of cancers. This term also refers to the medical specialty of cancer care, with particular reference to the use of radiotherapy or drugs to treat cancer. The medical specialty is often split into Clinical Oncology (doctors who use radiotherapy and drug treatment) and Medical Oncology (doctors who use drug treatment).

Palliative

Anything which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it.

Patient centred care

Care that is offered as a result of a partnership between the heathcare team and the person with the condition and their carers/family.

Percutaneous nephrostomy

See nephrostomy.

A procedure involving the insertion of a catheter, through the skin, into the kidney to drain urine when there is a blockage in the ureter or bladder.

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Photodynamic diagnosis (PDD)

The use of a specific agent to produce fluorescence when tissue is illuminated with light of a particular wavelength. Used in conjunction with cystoscopy by instillation of a photodynamic diagnosis agent into the bladder via a catheter, to try to identify cancer within the bladder.

Positron emission tomography (PET)

A specialised imaging technique using a radioactive tracer to produce a computerised image of body tissues and find abnormalities. PET scans may be used to help diagnose cancer, to see if it has spread and to investigate response to treatment.

Primary care

Services provided in a community setting, outside hospitals (secondary care), with which people usually have first contact.

Primary cystectomy

Surgical removal of the bladder as the initial treatment.

Primary tumour

Original site of the first cancer

Prognosis

A prediction of the likely outcome or course of a disease; the chance of recovery, recurrence or death.

Prognostic factors

Characteristics of a cancer or the person who has it, e.g. grade of tumour or co-morbidity, that influence the course of the disease under study.

Progressive disease

Cancer that is growing beyond the organ where it started. This is judged either by physical examination, scans, or blood tests.

Prophylaxis

The prevention of disease; preventative measures or treatment. Interventions to prevent an unwanted outcome.

Prospective Study

A study in which people are entered into research and then followed up over a period of time with future events recorded as they happen.

Psychosocial

Concerned with psychological or sociological influences on disease or other states

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Qualitative research

Research in which the outcomes are usually recorded in words, rather than with numbers. Often used to explore and understand peoples' beliefs, experiences, attitudes, behaviour and interactions.

Quality adjusted life years (QALYs)

A measure of health outcome which looks at both length of life and quality of life. QALYs are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a 0-1 scale). One QALY is equal to 1 year of life in perfect health, or 2 years at 50% health, and so on.

Quantitative research

Research which uses numerical measurement techniques (eg. measuring survival times after treatment).

Radical cystectomy

Surgical removal of the bladder. The lymph nodes in the pelvis are also removed. In men, the prostate is removed with the bladder, and in women, the womb, Fallopian tubes, ovaries, and part of the vagina are usually removed. Urinary drainage has to be re-established and this is done either by formation of a urinary stoma (ileal conduit) or bladder reconstruction.

Radical treatment

Treatment given with the aim of cure, rather than just improving symptoms or extending survival with the disease.

Radiosensitiser

A drug used at the same time as radiotherapy to increase the anticancer effect.

Radiotherapy

The use of radiation, usually x-rays or gamma rays, to kill cancer cells.

Randomised controlled trials (RCTs)

A type of experiment that is used to compare the effectiveness of different approaches, measures or treatments. The crucial feature of this form of trial is that people or groups are assigned at random to groups which receive the interventions being assessed or control treatments. RCTs offer the most reliable (i.e. least biased) form of evidence on effectiveness.

Recurrence

Recurrence is when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body.

Relapse

Where cancer starts to grow again after treatment.

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Retrograde stent

A plastic splint (stent) placed between the kidney and the bladder, within the body's own drainage pipe (the ureter), inserted via the bladder by doing a cystoscopy.

Rigid cystoscopy

Cystoscopy done using a rigid metal cystoscope, usually under general or spinal anaesthesia.

Sensitivity

The proportion of individuals with a disease who have that disease correctly identified by the study test

Sensitivity analysis

A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other setting. The analysis is repeated using different assumptions to examine the effect on the results.

Solitary papillary recurrence

A single recurrent cancer seen in the bladder at cystoscopy, in a person who has had bladder cancer in the past.

Specificity

The proportion of individuals who do not have a disease and who are correctly identified as not having it by the study test.

Staging Stage

The local extent of a cancer, in particular which parts of the organ of origin or adjacent organs are affected.

Survival

Survival is the time alive after diagnosis of a disease

Systematic review

A review of the literature carried out in order to address a defined question and using quantitative methods to summarise the results.

Systemic treatment

Treatment, usually given by mouth or by injection, that reaches and affects cancer cells throughout the body rather than targeting one specific area.

Transurethral resection (TUR)

Telescopic removal done using an adapted cystoscope called a resectoscope.

Transurethral resection of bladder tumour (TURBT)

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Telescopic removal of a new or recurrent bladder cancer, done using an adapted cystoscope called a resectoscope.

Ultrasound

A type of scan in which high-frequency sound waves are used to outline a part of the body.

Ureters

The body's normal tubes carrying urine from the kidneys to the bladder

Ureteric obstruction

A blockage in the ureters (for example by tumour or stone).

Urethra

The body's normal tube leading from the bladder through which urine leaves the body. In men the ureter exits at the tip of the penis, in women through the vulva.

Urinary stoma (ileal conduit)

An artificially created hole in the abdominal wall to allow drainage of urine from the kidneys (for example when the bladder has been removed).

Urography

An xray or scan which specifically outlines the kidneys, ureters and bladder.

Urological cancers

Cancers of the urinary tract. This term usually includes cancers of the kidney, ureter, bladder, prostate, penis and testicles.

Urology

A branch of medicine concerned with the diagnosis and treatment of diseases of the urinary organs in females and the urogenital system in males.

Urothelial cancer

Cancer arising from the urothelium.

Urothelium

The lining of the bladder, urethra, ureter and the collecting system of the kidney.

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Appendix E: Guideline scope

E.1 Guideline scope 2014

E.1.1 Guideline title

Bladder Cancer: The diagnosis and management of bladder cancer

E.1.1.1 Short title

Bladder cancer

E.1.2 The remit

The Department of Health has asked NICE to develop a clinical guideline on the diagnosis and management of bladder cancer.

E.1.3 Clinical need for the guideline

E.1.3.1 Epidemiology

- Bladder cancer is the 7th most common cancer in the UK. However, because it is more common in men than in women it is the 4th most common cancer in men and the 11th in women.
- In 2008, 9583 people were diagnosed with bladder cancer in England, Wales and Northern Ireland, and there were 2997 deaths from bladder cancer.
- About 80% of bladder cancers do not involve the muscle wall of the bladder (non-muscle invasive) at presentation and are confined to the urothelium and lamina propria of the bladder (stages pTa, pTis and pT1 respectively). Progression to more advanced disease from the pTa stage is uncommon and most pTa tumours are not life-threatening. However, recurrences are common and other areas of the urinary tract may be affected (renal pelvis, ureters and urethra). Progression from pT1 disease is more common, and occurs in up to 50% of cases.
- When bladder cancer invades bladder muscle it can spread rapidly beyond the bladder and is life-threatening. Even with optimal treatment, 5-year survival is only 50%.

E.1.3.2 Current practice

- Non-muscle invasive bladder cancers can recur and progress. Non-muscle invasive bladder cancer is divided into low-risk tumours (pTaG1 and most pTaG2) and high-risk tumours (some pTaG2, pTis, pTaG3 and pT1), based on the risk of progression. Recurrence is not life-threatening but progression is. Non-muscle invasive bladder cancer is usually treated with intravesical therapy after initial telescopic surgery. In low-risk tumours this is usually intravesical chemotherapy, and it reduces the risk of recurrence. In high-risk tumours this is usually intravesical immunotherapy (with Bacillus Calmette-Guérin, BCG), which reduces the risk of recurrence and may also reduce the risk of progression. Frequent hospital-based observation is also needed, often over many years.
- Muscle invasive bladder cancer needs intensive treatment that may include radical cystectomy, chemotherapy and radiotherapy. This can result in significant morbidity.
- The intensive treatment needed for muscle invasive bladder cancer and the prolonged hospital-based surveillance needed for non-muscle invasive bladder cancer mean that bladder cancer is one of the most expensive cancers to treat.

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- The significant disease and treatment-related morbidity, the substantial use of NHS resources and the wide variation in practice make a guideline on the diagnosis and management of bladder cancer a high priority. There is likely to be variation in current practice at every stage and with every intervention.

E.1.4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

E.1.5 Population

E.1.5.1 Groups that will be covered

- Adults (18 years and older) referred from primary care with suspected bladder cancer.
- Adults (18 years and older) with newly diagnosed bladder cancer (urothelial carcinoma, squamous carcinoma, adenocarcinoma and small-cell carcinoma).
- Adults (18 years and older) with newly diagnosed cancer of the urethra.
- Adults (18 years and older) with recurrent bladder or urethral cancer.
- Subgroups identified as needing specific consideration will be considered during development of the guideline.

E.1.5.2 Groups that will not be covered

- Adults with bladder sarcoma.
- Children (younger than 18 years).
- Adults with urothelial carcinoma of the ureter and renal pelvis.
- Adults with secondary cancers of the bladder or urethra (for example, colorectal cancer or cervical cancer invading the bladder).

E.1.6 Healthcare setting

All settings in which NHS-funded care is provided.

E.1.7 Clinical management

E.1.7.1 Key clinical issues that will be covered

- What are the information and support needs of patients with bladder cancer, for instance for people at the point of diagnosis, those considering options for treatment, and those considering palliative care?
- What is the most effective technology involving a urine test for identifying new and recurrent bladder cancer?
- What are the optimal endoscopic techniques for diagnosing new and recurrent bladder cancer (for example, the extent, depth and location of biopsies; white light, blue light, narrow-band cystoscopy)?
- What is the most effective imaging for staging newly diagnosed and recurrent bladder cancer (for example, ultrasound, CT, MRI)?

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- Which factors determine risk of relapse and progression in newly diagnosed non-muscle invasive bladder cancer (for example, histological grading of bladder cancer)?
- What are the comparative patient outcomes for treating low-risk non-muscle invasive bladder cancer with:
  - transurethral resection
  - intravesical chemotherapy
  - intravesical BCG?
- What are the comparative patient outcomes for treating high-risk non-muscle invasive bladder cancer with:
  - transurethral resection
  - intravesical chemotherapy
  - radiotherapy
  - intravesical BCG
  - radical cystectomy with urinary stoma or bladder reconstruction?
- What are the comparative patient outcomes for treating muscle invasive bladder cancer with:
  - radical cystectomy with urinary stoma or bladder reconstruction
  - radical radiotherapy (including a comparison of different radiotherapy schedules and chemoradiotherapy)
  - neo-adjuvant and adjuvant chemotherapy?
- What is the effect of smoking cessation on bladder cancer recurrence?
- What are the comparative patient outcomes for treating metastatic bladder cancer with:
  - first-line chemotherapy
  - second-line chemotherapy
  - radiotherapy
  - management of urinary tract obstruction?
- What is the optimum follow-up for patients with bladder cancer?
- What specific interventions are most effective for patients with intractable bleeding or bladder pain who are nearing the end of their lives (for example, nerve block, opioids, palliative radiotherapy, urinary diversion)?
- What specific interventions are most effective for patients with bladder toxicity following radiation or BCG therapy?

E.1.7.2 Clinical issues that will not be covered

- Referral from primary care with suspected bladder cancer, including haematuria [this will be covered by ‘Suspected cancer’, the update of ‘Referral guidelines for suspected cancer’ (NICE clinical guideline 27)].
- Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (this is the subject of an ongoing NICE technology appraisal).

E.1.8 Main outcomes

- Overall survival.
- Disease-free survival.
- Disease-related morbidity.
- Disease-related mortality.
- Treatment-related morbidity.
- Treatment-related mortality.

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- Psychological wellbeing.
- Quality of life for those nearing the end of their life.
- Number and length of admissions to hospital after diagnosis.
- Number and severity of adverse events.
- Health-related quality of life.

E.1.9 Review questions

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience.

Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

- What are the information and support needs of patients diagnosed with bladder cancer? (4.3.1a)
- What are the diagnostic accuracies of urine testing technologies for new and recurrent bladder cancer? (4.3.1b)
- What are the most effective endoscopic techniques for diagnosing bladder cancer (for example, the extent, depth and location of biopsies; white light, blue light, narrow band cystoscopy)? (4.3.1c)
- In the high- and low-risk subgroups of non-muscle invasive bladder cancer and in muscle invasive bladder cancer, what is the most appropriate method for staging newly diagnosed and recurrent disease? (4.3.1d)
- Which factors in newly diagnosed non-muscle invasive bladder cancer predict recurrence or progression after treatment? (4.3.1e)
- Does the extent of transurethral resection in non-muscle invasive bladder cancer reduce recurrence? (4.3.1f
- What are the most effective adjuvant intravesical therapy (chemotherapy or immunotherapy) regimens for low-risk and for high-risk non-muscle invasive bladder cancer? (4.3.1f, 4.3.1g)
- For which patients with non-muscle invasive bladder cancer would cystectomy produce better outcomes than BCG? (4.3.1g)
- For which patients with high risk non-muscle invasive bladder cancer would radiotherapy produce better outcomes than cystectomy? (4.3.1g)
- What are the optimal follow-up protocols for low-risk and high-risk non-muscle invasive bladder cancer? (4.3.1k)
- What is the optimal follow-up protocol for muscle invasive bladder cancer? (4.3.1k)
- For which patient groups with muscle invasive bladder cancer would radical cystectomy produce better outcomes than radical radiotherapy and for which groups would radical radiotherapy produce better outcomes? (4.3.1h)
- Is bladder reconstruction or urinary stoma the more effective method for urinary diversion? (4.3.1g, 4.3.1h)
- What is the optimal radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer? (4.3.1h)
- Which patients with bladder cancer should be offered neoadjuvant chemotherapy? (4.3.1h)
- Which patients with bladder cancer should be offered adjuvant chemotherapy? (4.3.1h)
- What is the optimal first-line chemotherapy regimen for patients with metastatic bladder cancer? (4.3.1j)

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- What is the optimal second-line chemotherapy regimen for patients with metastatic bladder cancer? (4.3.1j)
- What is the optimal radiotherapy regimen for patients with metastatic bladder cancer? (4.3.1j)
- What is the best way to manage urinary obstruction in patients with metastatic bladder cancer? (4.3.1j)
- Does smoking cessation affect outcomes for patients with bladder cancer? (4.3.1i)
- What specific interventions are most effective for patients with intractable bleeding or bladder pain who are nearing the end of their life (for example, nerve block, opioids, palliative radiotherapy, urinary diversion)? (4.3.1l)
- What specific interventions are most effective for patients with bladder toxicity following radiotherapy or BCG therapy for bladder cancer? (4.3.1m)

E.1.10 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

E.1.11 Status

E.1.11.1 Scope

This is the final scope.

E.1.11.2 Timing

The development of the guideline recommendations will begin in October 2012.

E.1.12 Related NICE guidance

E.1.12.1 Published guidance

NICE guidance to be updated

This guideline will not update or replace any NICE guidance.

NICE guidance to be incorporated

This guideline will not incorporate any NICE guidance.

Other related NICE guidance

- Opioids in palliative care. NICE clinical guideline 140 (2012).
- Patient experience in adult NHS services. NICE clinical guidance 138 (2012).
- Service user experience in adult mental health. NICE clinical guidance 136 (2011).
- Lower urinary tract symptoms. NICE clinical guideline 97 (2009).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Laparoscopic cystectomy. NICE interventional procedure guidance 287 (2009).
- Metastatic spinal cord compression. NICE clinical guideline 75 (2008).

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- Electrically-stimulated intravesical chemotherapy for superficial bladder cancer. NICE interventional procedure guidance 277 (2008).
- Intraoperative red blood cell salvage during radical prostatectomy or radical cystectomy. NICE interventional procedure guidance 258 (2008).
- Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer. NICE interventional procedure guidance 235 (2007).
- Urinary incontinence. NICE clinical guideline 40 (2006).
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).
- Improving outcomes in urological cancers. NICE cancer service guidance (2002).

E.1.12.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Referral guidelines for suspected cancer (update). NICE clinical guideline. Publication date to be confirmed.
- Denosumab for the treatment of bone metastases from solid tumours and multiple myeloma. NICE technology appraisal guidance. Publication date to be confirmed.
- Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract. NICE technology appraisal guidance. Publication date to be confirmed.

E.1.13 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'.

Information on the progress of the guideline will also be available from the NICE website.

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Appendix F: People and organisations involved in production of the guideline

F.1 Members of the Guideline Development Group

GDG Chair	
Professor Julia Verne	Chair, Director for Knowledge & Intelligence (South West), Public Health England
GDG Lead Clinician	
Mr William Turner	Lead Clinician, Consultant Urologist, Cambridge University Hospitals NHS Foundation Trust
Group Members	
Dr Robert Huddart	Reader in Urological Oncology and Honorary Consultant Clinical Oncologist, Institute of Cancer Research, Royal Marsden Hospital
Dr Ananya Choudhury	Consultant Clinical Oncologist, The Christie NHS Foundation Trust
Mr Hugh Mostafid	Consultant Urologist, North Hampshire Hospital
Professor James Catto	Professor of Urology, University of Sheffield and Honorary Consultant Urological Surgeon, Sheffield Teaching Hospitals
Dr Ashish Chandra	Consultant Uropathologist and Cytopathologist, Guy's and St. Thomas' Hospital NHS Foundation Trust
Dr Rob Jones	Reader and Honorary Consultant in Medical Oncology, University of Glasgow, Beatson West of Scotland Cancer Centre
Dr Jonathan Osborn	GP Partner, College Surgery Partnership, Cullompton, Devon
Dr Marcus Ben Taylor	Consultant Radiologist, The Christie NHS Foundation Trust
Ms Pauline Bagnall	Uro-oncology Nurse Specialist, Northumbria Healthcare NHS Foundation Trust, North Shields
Ms Helen Chilcott	Macmillan Uro-oncology Clinical Nurse Specialist, North Bristol NHS Trust, Bristol
Ms Louise Warren[q]	Patient/carer member
Mr Antony Miller[r]	Patient/carer member
Mr Phil Kelly	Patient/carer member

[q] From October 2012 to June 2013
[r] From June 2013 to February 2015

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Declarations of interest

GDG member	Interest declared	Type of Interest	Decisions Taken
William Turner	Project group member of Addenbrookes Urology patient information project (AUPIP) trying to improve shared and informed decision making	Personal non-pecuniary, non-specific	Declare and participate as topic area is not being investigating by guideline
William Turner	Lead of medical advisory group on Bladder cancer in the NHS right care programme, The decision aid is being developed by Totally Health	Personal non-pecuniary, non-specific	Declare and participate as topic area is not being investigating by guideline
Hugh Mostafid	Agreement with Kyowa to provide occasional advice on issues regarding intravesical chemotherapy. Agreement was formally terminated in February 2012.	Personal pecuniary, specific	Declare and withdraw from discussions on intravesical chemotherapy until February 2013.
Hugh Mostafid	Wife works on an ad-hoc basis as a marketing consultant for pharmaceutical company marketing new preparation of mitomycin.	Personal family interest, specific	Declare and withdraw from discussion on all topics regarding intravesical chemotherapy. 20.8.13 - This interest is no longer applicable as wife did not take up job.
Hugh Mostafid	Part of the trial management group for an NIHR funded trial on standard treatment with our without celecoxib for transitional cell bladder cancer. (BOXIT)	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Hugh Mostafid	Co-applicant on the trial management group for an NIHR funded trial comparing hyperthermia and mitomycin chemotherapy with a second BCG treatment or other standard treatment for bladder cancer.	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Hugh Mostafid	Chief investigator, involved in developing the trial protocol on a NIHR funded trial for standard surgical management of patients with low risk bladder cancer versus intravesical chemotherapy.	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Hugh Mostafid	Member of the NCRI bladder cancer clinical trials study group	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Hugh Mostafid	Founder member and trustee of Action on Bladder cancer, administrative role and patient education.	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Hugh Mostafid	Co-author of South West Surrey and Hampshire Cancer Network guidelines on bladder cancer.	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Jonathan Osborn	Director of Russell Osborn management company	Personal pecuniary, non-specific	Declare and participate as does not relate to healthcare industry
Jonathan	Director of Vosper International Ltd,	Personal	Declare and participate as

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GDG member	Interest declared	Type of Interest	Decisions Taken
Osborn	ship design company.	pecuniary, non-specific	does not relate to healthcare industry.
Marcus Ben Taylor	Received an honorarium in November 2011 from Novartis for lecture on recent advances and current strategies in GIST's	Personal pecuniary, non-specific	Declare and participate as GIST is not being investigated by the guideline.
Marcus Ben Taylor	Chief investigator, involved in developing trial protocol for a study of Buscopan to improve image quality in pelvic MRI. Funded by Christie Charitable Funds.	Non-personal pecuniary, non-specific	Declare and participate as image quality of MRI is not being investigated by the guideline.
Marcus Ben Taylor	Chief investigator, involved in developing trial protocol for a study on diffusion weighted imaging in pelvic MRI. Funded by radiology department, The Christie.	Non-personal pecuniary, non-specific	Declare and participate as diffusion weighted imaging of MRI is not being investigated by the guideline.
Marcus Ben Taylor	Member of the Royal College of Radiologists Guideline Group, involved in writing guideline for imaging of lymphoma.	Personal non-pecuniary	Declare and participate as lymphoma is not being investigated by the guideline.
Marcus Ben Taylor	Member of the NCAT reference group for peer review measures on carcinoma of unknown primary.	Personal non-pecuniary	Declare and participate as carcinoma of unknown primary is not being investigated by the guideline.
James Catto	Received honorarium from GlaxoSmithKline regarding the use of Dutasteride for prostate cancer	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
James Catto	Received honorarium for attending the scientific advisory board of Orion Pharma regarding the development of an agent to treat prostate cancer	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
James Catto	Received a research grant from GlaxoSmithKline for investigations of a novel therapeutic strategy in bladder cancer.	Non-personal pecuniary, non-specific	Declare and participate as novel therapeutic strategies are not being investigated by the guideline.
James Catto	Received a research grant from European Union, framework 7 for prostate cancer, profiling and evaluation of ncRNA, ProspeR.	Non-personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
James Catto	Received a research grant from Yorkshire cancer research for genetic instability and death in cancer cells.	Non-personal pecuniary, non-specific	Declare and participate as genetic instability and death in cancer cells is not being investigated by the guideline.
James Catto	Received a research grant from the urological foundation for investigation of microRNA medicated progression in urothelial cancer.	Non-personal pecuniary, non-specific	Declare and participate as microRNA medicated progression in urothelial cancer is not being investigated by the guideline.
James Catto	Received a research grant from Astellas for examination of the role of non-coding RNA in the mediation of chemoresistance in bladder cancer.	Non-personal pecuniary, non-specific	Declare and participate as of non-coding RNA in the mediation of chemoresistance in bladder cancer is not being investigated by the guideline.
James Catto	Received a research grant from the	Non-	Declare and participate as

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GDG member	Interest declared	Type of Interest	Decisions Taken
	urological foundation for an investigation of microRNA mediation progression in Urothelial cancer.	personal pecuniary, non-specific	microRNA medicated progression in urothelial cancer is not being investigated by the guideline.
James Catto	Received a research grant from Yorkshire cancer research for epigenetic carcinogenesis in the urothelium, development of a model system and examination of candidate occupational carcinogens.	Non-personal pecuniary, non-specific	Declare and participate as study area is not being investigated by the guideline.
James Catto	Received a research grant from the urological foundation for the loss of redundant mRNA export pathways in cancer cells, an investigation of this and novel therapeutic target and prognostic biomarker.	Non-personal pecuniary, non-specific	Declare and participate as study area is not being investigated by the guideline.
James Catto	Received a research grant from the Wellcome trust for the loss of redundant mRNA export pathways in cancer cells, an investigation of this and novel therapeutic target and prognostic biomarker.	Non-personal pecuniary, non-specific	Declare and participate as study area is not being investigated by the guideline.
James Catto	Received a research grant from Yorkshire Cancer Research for an investigation of the role of epigenetic silencing play in long non-coding of RNA expression in bladder cancer.	Non-personal pecuniary, non-specific	Declare and participate as study area is not being investigated by the guideline.
James Catto	Received an honorarium from Astellas for advisory board on Enzalutamide for prostate cancer.	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
James Catto	Received reimbursement of travel expenses from the Royal College of Radiologist to attend the 1st Royal College of Radiologists Bladder Cancer meeting in London and give a lecture on: Integrating biomarkers and imaging redesign management pathways – do we really need a transurethral resection in muscle invasive disease?	Personal pecuniary, non- specific	Declare and participate in discussion of all guideline topics as expenses were not beyond reasonable amounts
James Catto	Gave a lecture on updates in haematuria at the Urology and Men's Health Update in Sheffield	Personal non-pecuniary	Declare and participate in discussion of all guideline topics as no payment was received
James Catto	Received reimbursement of travel expenses from European Association of Urology to attend the 14th Society of Urological Oncology annual meeting and give a lecture on the management of high grade non-muscle invasive bladder cancer	Personal pecuniary, non-specific	Declare and participate in discussion of all guideline topics as expenses were not beyond reasonable amounts
Ashish Chandra	Presentation given on benign and malignant serous effusion cytology for the American Society of	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics

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GDG member	Interest declared	Type of Interest	Decisions Taken
	Cytopathology in November 2012		
Ashish Chandra	Co-Author of pathology dataset for bladder cancer.	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Ashish Chandra	Collaborator providing pathology input for the correlation of distribution of tumour in the prostate based histoscanning and comparing results on template biopsy and radical prostatectomy specimens. Funded by Kings College London.	Non-personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
Ashish Chandra	Collaborator providing pathology input for the trans-atlantic prostate group studies using tissue microarrays of prostate tissue collected retrospectively from a cohort of UK patients. Funded by Kings College London.	Non-personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
Ashish Chandra	Collaborator providing pathology input for evaluating the role of TMPRSS2-ERG antibody is predicting hormone sensitivity of prostate cancer and supervisor of the MSc project. Funded by Kings College London.	Non-personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
Ashish Chandra	Collaborator providing pathology input for a collaboration with Harvard University to explore the role of lipid metabolism in prostate cancer tissue microarrays from UK patients. Funded by Kings College London.	Non-personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
Ashish Chandra	Received expenses from Abbott for attending an advisory board looking at Bladder and prostate cancer testing.	Personal pecuniary, non-specific	Declare and participate as testing for bladder or prostate cancer is not being investigated by the guideline.
Ananya Choudhury	Received honorarium from Janssen for giving a lecture on prostate cancer in September 2011.	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
Ananya Choudhury	Received reimbursement of travel expenses from CRUK for attendance of an NCRI bladder clinical studies group meeting in November 2011.	Personal pecuniary, specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Ananya Choudhury	Received reimbursement of travel expenses from CRUK for attendance of an NCRI bladder clinical studies group meeting in November 2012.	Personal pecuniary, specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Ananya Choudhury	Received reimbursement of travel expenses from CRUK for attendance of a CT-Rad studies group meeting in November 2011	Personal pecuniary, non - specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Ananya Choudhury	Received reimbursement of travel expenses from CRUK for attendance of a CT-Rad studies	Personal pecuniary, non -	Declare and participate in discussions on all topics as expenses not beyond a

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GDG member	Interest declared	Type of Interest	Decisions Taken
	group meeting in June 2012.	specific	reasonable amount.
Ananya Choudhury	Received honorarium from Pierre Fabre for attending a discussion group on metastatic bladder cancer in August 2012.	Personal pecuniary, specific	Declare and withdraw from discussion on topics regarding metastatic bladder cancer until August 2013.
Ananya Choudhury	Principal investigator on the mainsail trial to evaluate the safety and effectiveness of lenalidomide in combination with docetaxel and prednisone for patients with castrate-resistant prostate cancer. Not involved in trial protocol and is funded by Celgene Corporation.	Non-personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigating by the guideline.
Ananya Choudhury	Principal investigator on the AFFIRM trial to evaluate the safety and efficacy of MDV3100 in patients with castrate-resistant prostate cancer, who have previously been treated with docetaxel-based chemotherapy. Not involved in trial protocol and is funded by Medivation Inc.	Non-personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigating by the guideline.
Ananya Choudhury	Chief investigator and involved in the trial protocol of the trial of the measurement of gemcitabine metabolites in blood and urine as predictors of response to GemX bladder radiotherapy. Funded by Christie Charitable Funds.	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Ananya Choudhury	Chief investigator and involved in the trial protocol of the trial of the simultaneous cone beam computed tomography (CBCT) acquisition during Arc radiotherapy in prostate cancer. Funded by Christie Charitable Funds.	Non-personal pecuniary, specific	Declare and participate as prostate cancer is not being investigating by the guideline.
Ananya Choudhury	Chief investigator and involved in the trial protocol of the trial on MRE11 as an outcome prediction biomarker in bladder cancer radiotherapy (MOBIBLART). Funded by Christie Charitable Funds.	Personal pecuniary, non-specific	Declare and participate as trial is not funded by health industry.
Ananya Choudhury	Chief investigator and involved in the trial protocol of a phase I feasibility study to compare early response assessment and planning volumes with contract-enhanced computer tomography (CT), MRI including diffusion weighted MRI (DWI) and dynamic-contrast enhanced (DCE) MRI in patients with limb sarcoma undergoing pre-operative radiotherapy. Funded by Christie Charitable Funds	Non-personal pecuniary, specific	Declare and participate as limb sarcoma is not being investigating by the guideline.
Ananya	Chief investigator for a study looking at the role of rectal balloons	Non-personal	Declare and participate as prostate cancer is not being

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GDG member	Interest declared	Type of Interest	Decisions Taken
Choudhury	in prostate radiotherapy (BRAD). Funded by Men Matter Charity.	pecuniary, specific	investigating by the guideline.
Ananya Choudhury	Member of the NCRI bladder clinical studies group	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Ananya Choudhury	Member of the CT-Rad group	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Ananya Choudhury	Member of the British Uro-Oncology Group	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Ananya Choudhury	Member of the European Society of Therapeutic Radiation Oncology.	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Ananya Choudhury	Author on publication in the journal Radiotherapy Oncology. Entitled: Necrosis predicts benefit from hypoxia-modifying therapy in patients with high risk bladder cancer enrolled in a phase III randomised trial.	Personal non-pecuniary, non-specific	Declare and participate as study area is not being investigated by the guideline.
Ananya Choudhury	Author of a chapter in a book (Treatment of Bladder Cancer) entitled: Bladder-sparing strategies for invasive bladder cancer.	Personal non-pecuniary, specific	Chair persons action to declare and participate in discussions on all topics.
Ananya Choudhury	Reviewed patient information on management of bladder cancer for NHS Choices.	Personal non-pecuniary, non-sspecific	Declare and participate as not specific.
Ananya Choudhury	Travel, accommodation and registration to attend ESTRO (European radiotherapy) in Amsterdam. Funding from Janssen.	Personal pecuniary, non-specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount
Rob Jones	Received an honorarium from Janssen for a consultancy on prostate cancer in November 2012	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from Janssen for speaking on prostate cancer in September 2012.	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from Pfizer for a consultancy on renal cancer in November 2012	Personal pecuniary, non-specific	Declare and participate as renal cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from Pfizer for speaking on renal cancer in June 2011.	Personal pecuniary, non-specific	Declare and participate as renal cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from Pfizer for speaking on renal cancer in October 2011.	Personal pecuniary, non-specific	Declare and participate as renal cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from Pfizer for speaking on renal cancer in November 2011	Personal pecuniary, non-specific	Declare and participate as renal cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from	Personal	Declare and participate as

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GDG member	Interest declared	Type of Interest	Decisions Taken
	Novartis for a consultancy on renal cancer in August 2012	pecuniary, non-specific	renal cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from Sanofi-Aventis for a consultancy on prostate cancer in November 2011.	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from Sanofi-Aventis for a consultancy on prostate cancer in July 2012.	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from Sanofi-Aventis for speaking on prostate cancer in October 2011.	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from GlaxoSmithKline for speaking on renal cancer in June 2012.	Personal pecuniary, non-specific	Declare and participate as renal cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from GlaxoSmithKline for speaking on renal cancer in November 2012	Personal pecuniary, non-specific	Declare and participate as renal cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from Astellas for a consultancy on renal cancer in March 2012.	Personal pecuniary, non-specific	Declare and participate as renal cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from AstraZeneca for a consultancy on the development of a non-marketed product in prostate cancer in January 2012.	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from AstraZeneca for a consultancy on prostate cancer in January 2012.	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from CureVac for a consultancy on prostate cancer in November 2012.	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by guideline.
Rob Jones	Received an honorarium from Roche for a consultancy on access to medicines in Scotland.	Personal pecuniary, non-specific	Declare and participate as access to medicines in Scotland is not being investigated by guideline.
Rob Jones	Received reimbursement of travel expenses from GlaxoSmithKline for attending ASCO which covered all aspects of medical treatment of cancer in May 2012.	Personal pecuniary, non-specific	Declare and participate as all aspects of medical treatment in cancer is not being investigated by guideline.
Rob Jones	Received reimbursement of travel expenses from GlaxoSmithKline for attending ESMO which covered all aspects of medical treatment of cancer in October 2012.	Personal pecuniary, non-specific	Declare and participate as all aspects of medical treatment in cancer are not being investigated by guideline.
Rob Jones	Received an honorarium from Dendreon for a consultancy on prostate cancer in November 2012.	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by guideline.
Rob Jones	Director of CRUK-CTU, which co-ordinates PLUTO trial.	Personal pecuniary, non-specific	Declare and withdraw from topics covering pazopanib vs weekly paclitaxel in relapsed or progressive TCC of urothelium in bladder cancer.
Rob Jones	Director of Beatson Clinical Trials	Non-	Declare and participate as no

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GDG member	Interest declared	Type of Interest	Decisions Taken
	unit which conducts trials for pharmaceutical and biotech companies, none relevant to bladder cancer in the past 12 months.	personal pecuniary, non-specific	trials related to bladder cancer.
Rob Jones	Chief investigator and involved in trials protocol on PLUTO trial, a randomised phase II study investigating pazopanib vs weekly paclitaxel in relapsed or progressive TCC of urothelium in bladder cancer. Part sponsored by GlaxoSmithKline and co-ordinated by CRUK	Non-personal pecuniary, specific	Declare and withdraw from topics covering pazopanib vs weekly paclitaxel in relapsed or progressive TCC of urothelium in bladder cancer.
Rob Jones	Local principal investigator for the LAMB trial, for lapatinib for people with bladder cancer which has spread and is a member of the trial management group. Part funded by GlaxoSmithKline.	Non-personal pecuniary, specific	Declare and participate as lapatinib is not being covered in guideline.
Rob Jones	Chief investigator and involved in trial protocol for TOUCAN trial, carboplatin, gemcitabine and vandetanib to treat TCC that has spread. Funded by AstraZeneca	Non-personal pecuniary, specific	Declare and withdraw from topics covering carboplatin, gemcitabine and vandetanib.
Rob Jones	Chief investigator for MAdCap, for prostate cancer, funded by Roche.	Non-personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
Rob Jones	Chief investigator for ASPEN, for renal cancer, funded by Novartis and Pfizer.	Non-personal pecuniary, non-specific	Declare and participate as renal cancer is not being investigated by the guideline.
Rob Jones	Presented data on Bladder cancer for a study funded by Topotargets.	Non-personal pecuniary, specific	Chair persons action to declare and participate in discussions on all topics
Rob Jones	Principal investigator on TOTEM trial to evaluate the addition of temsirolimus to the standard of 2-drug cisplatin/gemcitabine chemotherapy for first-line treatment of patients with advanced bladder cancer.	Non-personal pecuniary, specific	Declare and withdraw from discussions on any topic regarding cisplatin/gemcitabine for first line treatment of patients with advanced bladder cancer. (Chair decision that he can be asked questions)
Rob Jones	Principal investigator on SUCCINCT trial to evaluate the addition of sunitinib to standard 2-drug cisplatin/gemcitabine chemotherapy for first line treatment of patients with advanced bladder cancer.	Non-personal pecuniary, specific	Declare and withdraw from topics covering cisplatin/gemcitabine chemotherapy for first line treatment of bladder cancer.
Rob Jones	Principal investigator on trials not relating to Bladder cancer. Trials funded by Active Biotech research, Millennium/Takeda, Novartis, Pfizer, Sanofi-Aventis.	Non-personal pecuniary, non-specific	Declare and participate as trial in not related to bladder cancer.

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GDG member	Interest declared	Type of Interest	Decisions Taken
Rob Jones	On the editorial committee for the renal cancer clarity newsletter produced by the James Whale Fund.	Personal non-pecuniary	Declare and participate as renal cancer is not being investigated by the guideline.
Rob Jones	Reviews patient information leaflets and speaks at education meeting for Prostate Cancer UK, no payments are received.	Personal non-pecuniary	Declare and participate as prostate cancer is not being investigated by the guideline.
Rob Jones	Received an honorarium from Exelixis for consultancy advice on an emerging drug in bladder cancer.	Personal pecuniary, non-specific	Declare and participate as emerging drugs for bladder cancer are not being investigated by the guideline.
Rob Jones	Received an honorarium from Astellas for consultancy on prostate cancer..	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
Rob Jones	Received an honorarium from Bayer for consultancy advice on the use of sorafenib in renal cell carcinoma.	Personal pecuniary, non-specific	Declare and participate as in renal cell carcinoma is not being investigated by the guideline.
Rob Jones	Received payment from Bristol-Myers Squibb for consultancy regarding immunotherapy in renal cancer	Personal pecuniary, non-specific	Declare and participate as renal cancer is not being investigated by the guideline.
Robert Huddart	Received an honorarium from Stratagem for attending an advisory board on the treatment of radiation cystitis.	Personal pecuniary, non-specific	Declare and participate as radiation cystitis is not being investigated by the guideline.
Robert Huddart	Received payment for management of bladder cancer education session from Pierre Fabre.	Personal pecuniary, non-specific	Declare and participate as guideline is covering specific aspects of bladder cancer management.
Robert Huddart	Received an honorarium from MA Healthcare Ltd for giving a case presentation on the management of bladder cancer patients at a renal and bladder conference	Personal pecuniary, specific	Declare and participate as guideline is covering specific aspects of bladder cancer management.
Robert Huddart	Received subsistence expenses from Janssen for attending a conference on abiratirone for prostate cancer	Personal pecuniary, non-specific	Declare and participate as prostate cancer is not being investigated by the guideline.
Robert Huddart	Chief investigator, and involved in designing the trial protocol of BC2001 trial, a randomised phase III study of radiotherapy with and without synchronous chemotherapy in muscle invasive bladder cancer. Funded by CRUK	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Robert Huddart	Chief investigator, and involved in designing the trial protocol of SPARE trial, a randomised selective bladder preservation against radical excision in muscle invasive transitional cell carcinoma of the bladder. Funded by CRUK	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Robert	Chief investigator, and involved in	Non-	Declare and participate as

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GDG member	Interest declared	Type of Interest	Decisions Taken
Huddart	designing the trial protocol of IDEAL trial for image guided dose escalated adaptive bladder radiotherapy. Funded by CRUK and Royal College of Radiologists.	personal pecuniary, specific	trial is not funded by health industry.
Robert Huddart	Chief investigator, and involved in designing the trial protocol for hypofractionated radiotherapy in bladder cancer. Funded by NIHR.	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Robert Huddart	Chief investigator, and involved in designing the trial protocol for IMRT for bladder cancer. Funded by NIHR.	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Robert Huddart	Co-investigator, involved in developing trial protocol, the application for funding and on trial management group of BOXIT trial, for the standard treatment with or without celecoxib for transitional cell bladder cancer. Funded by CRUK	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Robert Huddart	Co-investigator, involved in trial application of ToTem study a phase I/II single-arm trial to evaluate the combination of cisplatin and gemcitabine with the mTOR inhibitor temsirolimus for first-line treatment of patients with advanced transitional cell carcinoma of the urothelium. Funded by CRUK.	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Robert Huddart	Principal investigator for SUCCINCT trial looking at the addition of sunitinib to standard 2-drug cisplatin/gemcitabine chemotherapy for first line treatment of patients with advanced bladder cancer. Funded by CRUK	Non-personal pecuniary, specific	Declare and participate as trial is not funded by health industry.
Robert Huddart	Local principal investigator for TOUCAN, a randomised phase II trial of carboplatin and gemcitabine +/- vandetanib in first line treatment of advanced urothelial cancer in patients who are not suitable to receive cisplatin. Funded by CRUK and AstraZeneca.	Non-personal pecuniary, specific	Declare and participate in discussions on all topics as only the principal investigator and therefore not involved in designing the trial protocol.
Robert Huddart	Local principal investigator for LAMB a phase II/III randomised two arm trial comparison of maintenance lapatinib versus placebo after first line chemotherapy in patients with HER1 and/or HER2 over expressing locally advanced or metastatic bladder cancer. Funded by CRUK and AstraZeneca.	Non-personal pecuniary, specific	Declare and participate in all topics as maintenance lapatinib versus placebo is not being covered in the guideline.
Robert Huddart	Local principal investigator for POUT, a peri-operative chemotherapy or surveillance in	Non-personal pecuniary,	Declare and participate as trial is not funded by health

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GDG member	Interest declared	Type of Interest	Decisions Taken
	upper tract urothelial cancer trial. Funded by CRUK	specific	industry.
Robert Huddart	Chief investigator of CRUK TE22 & TE23 national testicular genetic genome wide association study	Non-personal pecuniary, non-specific	Declare and participate as study area is not being investigated by guideline.
Robert Huddart	Co-investigator of TRIST trial of seminoma surveillance	Non-personal pecuniary, non-specific	Declare and participate as study area is not being investigated by guideline.
Robert Huddart	Co-investigator of GEM-TIP trial of salvage testis chemotherapy.	Non-personal pecuniary, non-specific	Declare and participate as study area is not being investigated by guideline.
Robert Huddart	Co-investigator of 111 study, of adjuvant chemotherapy in NSGCT.	Non-personal pecuniary, non-specific	Declare and participate as study area is not being investigated by guideline.
Robert Huddart	Co-investigator of TRYMS trial of hormone replacement in cancer survivors.	Non-personal pecuniary, non-specific	Declare and participate as study area is not being investigated by guideline.
Robert Huddart	Member/trustee of British Uro Oncology group	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Robert Huddart	Published research articles relating to bladder cancer treatment specifically a trial that showed to improve outcome for chemo-radiotherapy over radiotherapy and has publically stated that this should be the standard of care.	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Robert Huddart	Member of the NCRI bladder cancer studies group	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Robert Huddart	Member of the NCIN urology site specific clinical reference group, representing testis	Personal non-pecuniary	Declare and participate as study area is not being investigated by guideline.
Robert Huddart	Presentation at NCRI urology meeting on the BC2001 trial (no payment or expenses received).	Personal non-pecuniary, Specific	Declare and participate as trial is not funded by health industry.
Robert Huddart	Travel expenses for a presentation on ‘How should IMRT and IGRT be used in bladder radiotherapy’ at a Bladder Cancer Meeting hosted by The Royal College of Radiologists.	Personal pecuniary, non-specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Robert Huddart	Travel expenses for a presentation on ‘Advances in the non-surgical management of bladder cancer’ at a conference hosted by The Royal College of Radiologists.	Personal pecuniary, non-specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Robert Huddart	Invited to be a local site principal investigator for a new neo-adjuvant chemotherapy trial funded by NCRI	Personal non-pecuniary,	Declare and can participate in discussion on all topics as trial is not funded by the

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GDG member	Interest declared	Type of Interest	Decisions Taken
	(no remuneration).	specific	healthcare industry.
Robert Huddart	Chief investigator of RAIDER trial (A randomised phase II trial of adaptive image guided standard or dose escalated tumour boost radiotherapy in the treatment of transitional cell carcinoma of the bladder). Funded by Cancer Research UK	Non-personal pecuniary, specific	Declare and can participate in discussion on all topics as trial is not funded by the healthcare industry.
Robert Huddart	Chief investigator of HYBRID trial (A multicentre randomised phase II study of hypofractionated bladder radiotherapy with or without image guided adaptive planning in patients with muscle invasive bladder cancer). Funded by Cancer Research UK	Non-personal pecuniary, specific	Declare and can participate in discussion on all topics as trial is not funded by the healthcare industry.
Robert Huddart	Received reimbursement of travel expenses from Janssen Pharmaceuticals to attend ASCO in June 2014	Personal pecuniary, non-specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Robert Huddart	Invited to speak on bladder cancer radiotherapy at the East Anglian Bladder meeting in October 2014. No fee received.	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Robert Huddart	Spoke on bladder cancer image guided radiotherapy at Royal College of Radiologists meetings in April and June 2014. No fee received	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics
Robert Huddart	Has been invited to talk on the RAIDER trial at the Australian Radiotherapy/Cancer meeting in September 2014. will be receiving reimbursement of travel expenses and an honorarium from Astra Zeneca.	Personal pecuniary	Decalre and withdraw from discussion of any topics which involve interventions manufactured by Astra Zeneca.
Pauline Bagnall	Honorarium and travel to present on 'An overview and update on bladder cancer and management guidelines' for urology nurses. Funded by MSD.	Personal pecuniary, non-specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Helen Chilcott	Honorarium received for a talk entitled 'Prostate Cancer - Long Term Condition & Survivorship' for GPs. Paid for by AstraZeneca.	Personal pecuniary, nonspecific	Declare and participate as prostate cancer is not being investigated by the guideline. The event did not go ahead but honorarium was still paid.
Phil Kelly	Lay representative on the NICE Staffing Levels Advisory Committee (SLAC) for the first guideline 'Safe nurse staffing of adult wards in acute hospitals'. Attendance fee and expenses.	Personal pecuniary, non-specific	Declare and participate as not specific.
Louise	None declared		

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GDG member	Interest declared	Type of Interest	Decisions Taken
Warren			
Antony Miller	None declared		

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F.2 Organisations invited to comment on the guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

Abbott Molecular	British Psychological Society
Abertawe Bro Morgannwg University Health Board	British Red Cross
Action on Bladder Cancer	British Society of Interventional Radiology
ADDEPT	British Uro-Oncology Group
Aintree University Hospital NHS Foundation Trust	Caduceus Support Limited
Alere Ltd	Cambridge University Hospitals NHS Foundation Trust
Allergan Ltd UK	Camden Carers Centre
Alliance Pharmaceuticals	Camden Link
Allocate Software PLC	Cancer Commissioning Team
American Medical Systems Inc.	Cancer National Specialist Advisory Group
American Medical Systems UK Ltd	Cancer Phytotherapy Service
Amgen UK	Cancer Research UK
Aspire Pharma	Cancer52
Association for Palliative Medicine of Great Britain	Capsulation PPS
Association of Anaesthetists of Great Britain and Ireland	Care Not Killing Alliance
Association of British Insurers	Care Quality Commission
Association of Chartered Physiotherapists in Oncology and Palliative Care	Central Manchester and Manchester Children's Hospital NHS Trust
Astrazeneca UK Ltd	Cepheid Uk Ltd
Barnsley Hospital NHS Foundation Trust	Chartered Physiotherapists Promoting Continence
BASO-The Association for Cancer Surgery	Chartered Society of Physiotherapy
Belfast Health and Social Care Trust	Cheshire and Merseyside SCN
Bladder and Bowel Foundation	Clarity Informatics Ltd
Bladder Cancer Support UK	CLIC Sargent
Boehringer Ingelheim	Coloplast Limited
British Association for Cytopathology	Covidien Ltd.
British Association of Urological Surgeons	Croydon Clinical Commissioning Group
British Dietetic Association	Croydon Health Services NHS Trust
British Medical Association	Croydon University Hospital
British Medical Journal	CWHHE Collaborative CCGs
British Medical Ultrasound Society	Deltex Medical
British National Formulary	Department of Health
British Nuclear Cardiology Society	Department of Health, Social Services and Public Safety - Northern Ireland
British Nuclear Medicine Society	East and North Hertfordshire NHS Trust
British Pain Society	East Kent Hospitals University NHS Foundation Trust

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CWHHE Collaborative CCGs	Mid Yorkshire Hospitals NHS Trust
Deltex Medical	Midlands Centre for Spinal Injuries
Department of Health	Milton Keynes Hospital NHS Foundation Trust
Department of Health, Social Services and Public Safety - Northern Ireland	Ministry of Defence (MOD)
East and North Hertfordshire NHS Trust	Monash Health
East Kent Hospitals University NHS Foundation Trust	National Association of Primary Care
Economic and Social Research Council	National Cancer Action Team
Ethical Medicines Industry Group	National Cancer Intelligence Network
Five Boroughs Partnership NHS Trust	National Clinical Guideline Centre
GfK Bridgehead	National Collaborating Centre for Cancer
GP update / Red Whale	National Collaborating Centre for Mental Health
Greater Manchester, Lancashire and South Cumbria Strategic Clinical Network	National Collaborating Centre for Women's and Children's Health
Health & Social Care Information Centre	National Council for Palliative Care
Health and Care Professions Council	National Deaf Children's Society
Healthcare Improvement Scotland	National Institute for Health Research Health Technology Assessment Programme
Healthcare Infection Society	National Institute for Health Research
Healthcare Quality Improvement Partnership	National Patient Safety Agency
Healthwatch East Sussex	NHS Barnsley Clinical Commissioning Group
Help Adolescents With Cancer	NHS Choices
Herts Valleys Clinical Commissioning Group	NHS Coastal West Sussex CCG
Hinchingbrooke Healthcare NHS Trust	NHS Connecting for Health
Hindu Council UK	NHS County Durham and Darlington
Hockley Medical Practice	NHS Cumbria Clinical Commissioning Group
Humber NHS Foundation Trust	NHS England
Independent Healthcare Advisory Services	NHS Hardwick CCG
Institute of Biomedical Science	NHS Health at Work
Integrity Care Services Ltd.	NHS Improvement
Intuitive Surgical	NHS Medway Clinical Commissioning Group
Ipsen Ltd	NHS Plus
Isabel Hospice	NHS Sheffield
Johnson & Johnson Medical Ltd	NHS South Cheshire CCG
King's College Hospital NHS Foundation Trust	NHS Wakefield CCG
Lancashire Care NHS Foundation Trust	NHS Warwickshire North CCG
Local Government Association	Nordic Pharma
London Cancer	North Essex Partnership Foundation Trust
London cancer alliance	North of England Commissioning Support
Luton and Dunstable Hospital NHS Trust	North West London Hospitals NHS Trust
MacGregor Healthcare	Northern Health and Social Care Trust
Macmillan Cancer Support	Nottingham City Council
Medicines and Healthcare products Regulatory Agency	Nottingham University Hospital NHS Trust
Merck Sharp & Dohme UK Ltd	Nova Healthcare
Mid Cheshire Hospitals NHS Trust	Nursing and Midwifery Council
	Oxford Health NHS Foundation Trust

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Oxfordshire Clinical Commissioning Group	Royal Pharmaceutical Society
Parenteral and Enteral Nutrition Group	Royal Society of Medicine
Partneriaeth Prifysgol Abertawe	Royal Surrey County Hospital NHS Trust
Pathfinders Specialist and Complex Care	Salford Royal NHS Foundation Trust
Pelvic Obstetric and Gynaecological Physiotherapy	Sandoz Ltd
Pfizer	Sanofi
PHE Alcohol and Drugs, Health & Wellbeing Directorate	Scottish Intercollegiate Guidelines Network
Pierre Fabre Ltd	Sheffield Children's Hospital
PrescQIPP NHS Programme	Sheffield Teaching Hospitals NHS Foundation Trust
Primary Care Pharmacists Association	Social Care Institute for Excellence
Primrose Bank Medical Centre	Society and College of Radiographers
Public Health Agency for Northern Ireland	South Eastern Health and Social Care Trust
Public Health England	South London & Maudsley NHS Trust
Public Health Wales NHS Trust	South Tees Hospitals NHS Trust
Public Health Wales NHS Trust	South West Yorkshire Partnership NHS Foundation Trust
Queen Elizabeth Hospital King's Lynn NHS Trust	Southern Health & Social Care Trust
Queen's University Belfast	Southport and Ormskirk Hospital NHS Trust
Randox Laboratories Limited	Spectranetics Corporation
Rarer Cancers Foundation	St Mary's Hospital
Roche Diagnostics	Staffordshire and Stoke on Trent Partnership NHS Trust
Roche Products	Stockport Clinical Commissioning Group
Royal College of Anaesthetists	Tameside Hospital NHS Foundation Trust
Royal College of General Practitioners	Tenovus
Royal College of General Practitioners in Wales	Tenovus The Cancer Charity
Royal College of Midwives	Teva UK
Royal College of Midwives	The African Eye Trust
Royal College of Nursing	The Association for Cancer Surgery
Royal College of Obstetricians and Gynaecologists	The Institute of Cancer Research
Royal College of Paediatrics and Child Health	The Patients Association
Royal College of Pathologists	UCL Partners
Royal College of Physicians	UHS NHS Foundation Trust
Royal College of Physicians and Surgeons of Glasgow	UK National Screening Committee
Royal College of Psychiatrists	United Lincolnshire Hospitals NHS
Royal College of Radiologists	University Hospital Birmingham NHS Foundation Trust
Royal College of Surgeons of Edinburgh	University Hospital Southampton NHS Foundation Trust
Royal College of Surgeons of England	University Hospitals Birmingham
Royal Cornwall Hospitals NHS Trust	Urostomy Association
Royal Derby Hospital	Velindre NHS Trust
Royal Free London NHS Foundation Trust	Walsall Local Involvement Network

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Welsh Government	Westminster Local Involvement Network
Welsh Scientific Advisory Committee	Wigan Borough Clinical Commissioning Group
West Suffolk Hospital NHS Trust	Wirral University Teaching Hospital NHS Foundation Trust
Western Health and Social Care Trust	York Hospitals NHS Foundation Trust
Western Sussex Hospitals NHS Trust	Yorkshire and Humber Strategic Clinical Network

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F.3 Individuals carrying our literature reviews and complementary work

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s From September 2012 to September 2013
t From September 2013 to March 2014
u From March 2014

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F.4 Expert advisors to the Guideline Development Group

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