National Collaborating Centre for Cancer

Prostate Cancer:

diagnosis and treatment

Clinical Guideline

Full Guideline

July 2013

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence

Funding
Funded to produce guidelines for the NHS by NICE

This guidance is an update of NICE clinical guideline 58 (published February 2008) and will replace it.

New and updated recommendations have been included on the diagnosis and treatment of men with prostate cancer

Where recommendations are shaded in grey and end **[2008]** the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.

You are invited to comment on the new and updated recommendations in this guideline only. These are marked as **[2014]** if the evidence has been reviewed but no change has been made to the recommendation, or **[new 2014]** if the evidence has been reviewed and the recommendation have been added or updated.

Appendix K contains recommendations from the **[2008]** guideline that NICE proposes deleting in the 2014 update. This is because the evidence has been reviewed and the recommendation has been updated or because NICE has updated other relevant guidance and has replaced the original recommendations. Where there are replacement recommendations, details are provided. Where there is no replacement recommendation, an explanation for the proposed deletion is given. You are invited to comment on the deleted recommendations as part of the consultation on the 2014 update.

The original NICE guideline and supporting documents are available from www.nice.org.uk/guidance/CG58

Contents

Update 2014

Update 2014

Update 2014

Update 2014

Update 2014

Update 2014

Update 2014

Update 2014

Update 2014

Update 2014

Update 2014

Foreword

The original Prostate Cancer: Diagnosis and Treatment Guideline published in 2008 was the first clinical guideline produced by the National Collaborating Centre for Cancer (NCC-C); accordingly this is now the first NCC-C clinical guideline to be reviewed and updated. Many areas of the original guideline are unchanged as there is little or no new evidence; other aspects have been completely rewritten. As ever there are still many topics where the research evidence is incomplete or conflicting, and so the Guideline Development Group (GDG) have been required to reach a consensus using the evidence available to them in several areas. In places where it was clear that further work needed to be done, new research recommendations have been made which we hope will be used as the basis for future research work.

We are both grateful for the commitment shown by all members of the GDG who have worked very hard over the last two years to put this document together. We would also like to thank the staff of the NCC-C in Cardiff for providing great support and guidance throughout the process; without their tireless work this document could not have been delivered on time.

Finally, we would like to acknowledge the work of Sean Duffy, who was originally appointed as the Chair of the GDG, but who had to leave that post in April 2013 on his appointment as the new National Clinical Director for Cancer.

John Graham, NCC-C Director (GDG Chair Prostate Cancer Update from March 2013)

Peter Kirkbride, GDG Clinical Lead Prostate Cancer Update

Update 2014

Key priorities for implementation

- **Discuss all relevant management options recommended in this guideline with men with prostate cancer and their partners or carers, irrespective of whether they are available through local services. [2008]**

- **Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound 10–12 core biopsy to determine whether another biopsy is needed. [new 2014]**

- **Consider multiparametric MRI, or CT if MRI is contraindicated, for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. [new 2014]**

- **Offer active surveillance as an option to men with low-risk localised prostate cancer for whom radical surgery or radiotherapy is suitable. [new 2014]**

- **Consider active surveillance for men with intermediate-risk localised prostate cancer who do not wish to have immediate radical treatment. [new 2014]**

- **Consider using the following protocol for men who have chosen active surveillance. [new 2014]**

Timing	Tests[a]
At enrolment in active surveillance	**Multiparametric MRI if not previously performed**
Year 1 of active surveillance	**Every 3–4 months: measure PSA[b]** **Throughout active surveillance: monitor PSA kinetics[c]** **Every 6–12 months: DRE[d]** **At 12 months: prostate re-biopsy**
Years 2–4 of active surveillance	**Every 3–6 months: measure PSA[b]** **Throughout active surveillance: monitor PSA kinetics[c]** **Every 6–12 months: DRE[d]**
Year 5 and every year thereafter until active surveillance ends	**Every 6 months: measure PSA[b]** **Throughout active surveillance: monitor PSA kinetics[c]** **Every 12 months: DRE[d]**

a If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or rebiopsy
b May be carried out in primary care if there are agreed shared-care protocols and recall systems
c May include PSA doubling time and velocity
d Should be performed by a healthcare professional with expertise and confidence in performing DRE

- **Ensure that men with signs or symptoms of radiation-induced enteropathy are offered care from a team of professionals with expertise in radiation-induced enteropathy (who may include oncologists, gastroenterologists, bowel surgeons, dietitians and specialist nurses). [new 2014]**

- **Ensure that men have early and ongoing access to specialist erectile dysfunction services. [2008, amended 2014]**

Update 2014

- **Offer men with intermediate- and high-risk localised prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone. [new 2014]**

- **Consider intermittent therapy for men having long-term androgen deprivation therapy (not in the adjuvant setting), and include discussion with the man, and his family or carers if he wishes, about:**
    - **i. the rationale for intermittent therapy and**
    - **ii. the limited evidence for reduction in side effects from intermittent therapy and**
    - **iii. the effect of intermittent therapy on progression of prostate cancer. [new 2014]**

Update 2014

Key research recommendations

- **Further research is required into the identification of prognostic indicators in order to differentiate effectively between men who may die with prostate cancer and those who might die from prostate cancer [2008].**

- **What is the effectiveness of androgen deprivation therapy or brachytherapy, in combination with radiotherapy, for men with intermediate- and high-risk localised non-metastatic prostate cancer? [2014]**

- **Clinical trials should be set up to examine the effect of local salvage therapies on survival and quality of life in men with biochemical relapse after radiotherapy [2008].**

- **What is the clinical and cost effectiveness of standard care with bisphosphonates compared with denosumab to treat osteoporosis caused by long-term androgen deprivation therapy? [2014]**

- **What is the effectiveness of continuous compared with 12 weeks of supervised aerobic resistance in reducing fatigue in men receiving androgen deprivation therapy? [2014].**

Update 2014

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.

Updating a NICE clinical guideline

Guidelines developed by NICE are published with the expectation that they will be reviewed and updated as is considered necessary. In April 2011, the National Collaborating Centre for Cancer (NCC-C) was asked by NICE to conduct a review of CG58 to determine if an update was required. This review was conducted in accordance with the NICE guideline development process (NICE 2009, 2012) and required a search for new evidence, using versions of the original search strategies, seeking views of past Guideline Development Group (GDG) members, and the collation of feedback on the guideline post publication. Based on these sources of information, the NCC-C prepared a review proposal identifying which areas of CG58 required updating. This document was then subject to consultation with registered stakeholders. Based on their feedback NICE decided that CG58 needed updating.

In July 2011 the National Collaborating Centre for Cancer (NCC-C) was asked by NICE to update CG58 in accordance with the NICE guideline development process outlined in the 2009 and 2012 editions of the guidelines manual (NICE 2009, 2012).

This guideline updates and replaces CG58. Any sections of CG58 that have not been amended are integrated within this updated document. Changes in NICE guideline development methodology since 2008 mean the way information is presented may, at times be inconsistent (for example, the style of evidence presentation). Recommendations are marked **[2008]**, **[2014]** or **[new 2014]** to indicate the year of the last evidence review:

- **[2008]** indicates that the evidence has not been updated and reviewed since 2008
- **[2014]** indicates that the evidence has been updated and reviewed but no changes to the 2008 recommendation has been made
- **[new 2014]** indicates that the evidence has been reviewed and a new recommendation has been made.

All supporting text from updated and new topics presented in this guideline have been highlighted. The background text which accompanies recommendations from CG58 has been revised to reflect current practice.

Update 2014

Who is the Guideline Intended For?

This guideline does not include recommendations covering every detail of the diagnosis and treatment of prostate 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 men with prostate cancer, as well as to the men 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 men.

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 2009, 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 prostate cancer guideline can be found in Appendix I.

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 2009, 2012). A team of health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG) (Appendix I), 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
- 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
- updating the guideline.

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 2009, 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

Update 2014

- 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 H. 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 prostate cancer GDG was recruited in line with the 'NICE guidelines manual' (NICE 2009, 2012). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and shortlisted candidates were interviewed by telephone 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 organistations/charities (Appendix I). Individual GDG members were selected 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 the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix I).

Update 2014

Guideline Development Group Meetings

Ten GDG meetings were held between 9-10 February 2012 and 1-2 May 2013. 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 prostate 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 CG58 the GDG identified areas where there was a requirement for expert input on particular specialist clinical questions. The clinical questions were addressed by either the production of a position paper or a formal presentation by a recognised expert who had been identified via the relevant registered stakeholder organisation.

A full list of recognised experts who contributed to CG58 can be found in Appendix I. All relevant position papers are presented as part of the evidence review. No expert advisers contributed to the development of the update.

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). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated.

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), 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 researched (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.

Update 2014

Table 1: Components of the review protocol

Component	Description
Clinical question	The clinical question as agreed by the GDG
Objectives	Short description; for example 'To estimate the effects and cost effectiveness of...' or 'To estimate the diagnostic accuracy of...'
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework. 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').

For those clinical topics that were updated from the 2008 guideline, searches were set to only identify evidence published after June 2007 to ensure no relevant papers were missed. No date limits were applied to searches carried on new topics within the 2014 guideline.

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).

Update 2014

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
- (SCI-EXPANDED) 1899 onwards and Social SciencesCitation Index (SSCI) 1956 onwards]
- System for Information on Grey Literature In Europe (SIGLE) 1980–2005
- Biomed Central 1997 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
- British Nursing Index (BNI) 1993 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 8-10 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, May 2013 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 on the type of population, intervention, comparator and outcomes (PICO) 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 a modification of GRADE (NICE 2009, 2012; http://gradewordinggroup.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 topic 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 tan unexplained heterogeneity of results
Indirectness	Indirectness refers so 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
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

Update 2014

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2009, 2012). In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

For non-interventional questions, for example the questions regarding diagnostic test accuracy, a narrative summary of the quality of the evidence was given. The quality of individual diagnostic accuracy studies was assessed using the QUADAS tool (Whiting, *et al*., 2003).

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 men with prostate 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 prostate 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 2009, 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
- 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

For each topic, a review of the economic literature was conducted. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics filter.

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

Update 2014

- 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 2009, 2012).

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE 2009, 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

Update 2014

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

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 are several published technology appraisals (TA) which are relevant to this guideline (TA101, TA194, TA255, TA259, TA265 - see www.nice.org.uk/TA/published). In line with NICE methodology, the recommendations from these TAs have either been reproduced verbatim in the prostate cancer guideline or cross referenced.

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 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
- ‘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. Recommendations in the 2008 guideline were accompanied by a ‘qualifying statement’ which stated the level of evidence the recommendations were based on. To make this process more transparent to the reader, NICE have introduced an explicit, easily

Update 2014

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 I) had one opportunity to comment on the draft guideline which was posted on the NICE website between 16 July 2013 and 10 September 2013 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 prostate cancer guideline which are available from the NICE website:

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 14 May 2013 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Update 2014

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.

Update 2014

References

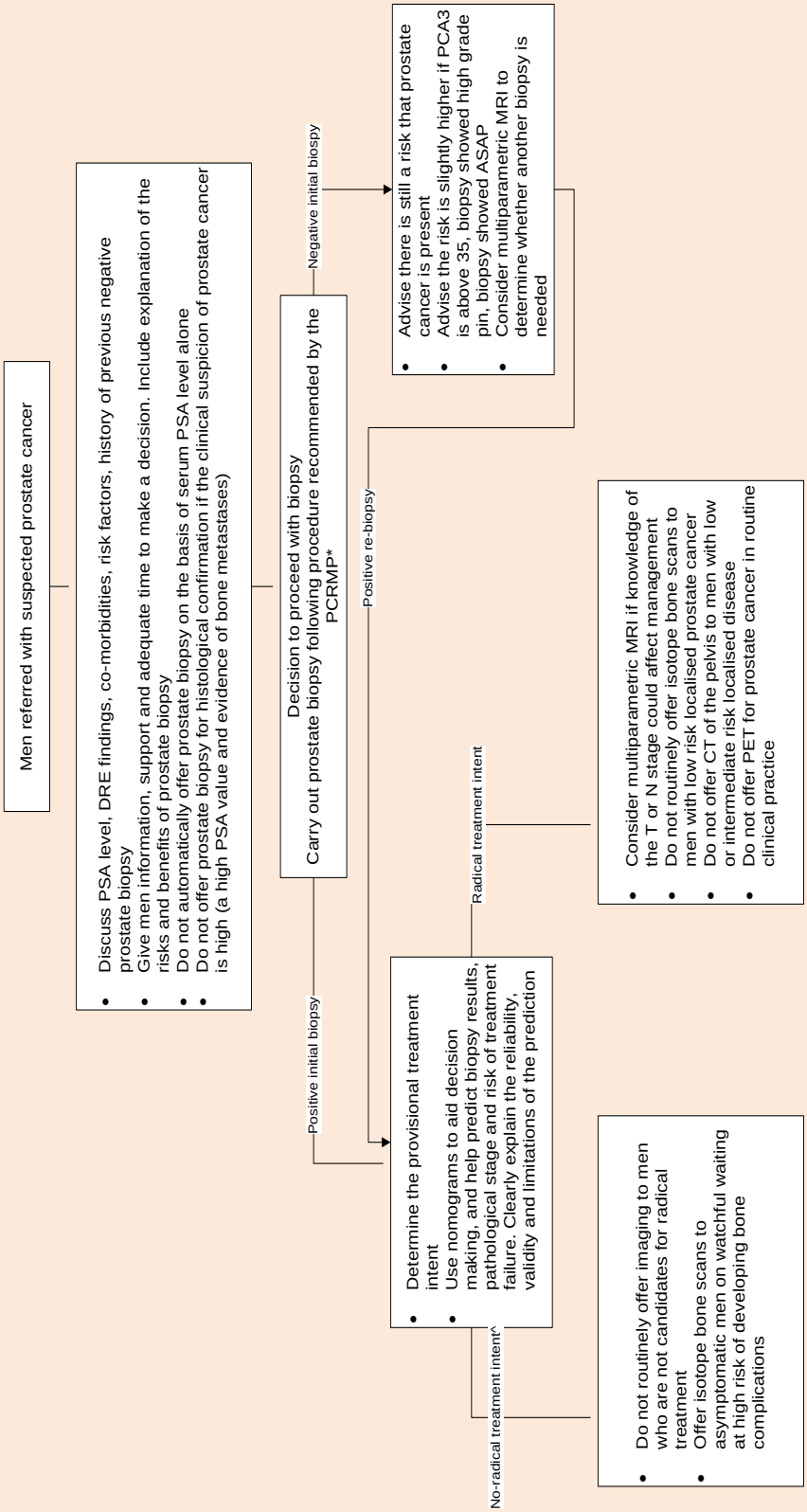
National Institute for Health and Clinical Excellence (2009) The guidelines manual. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidelinesmanual

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.

Algorithms

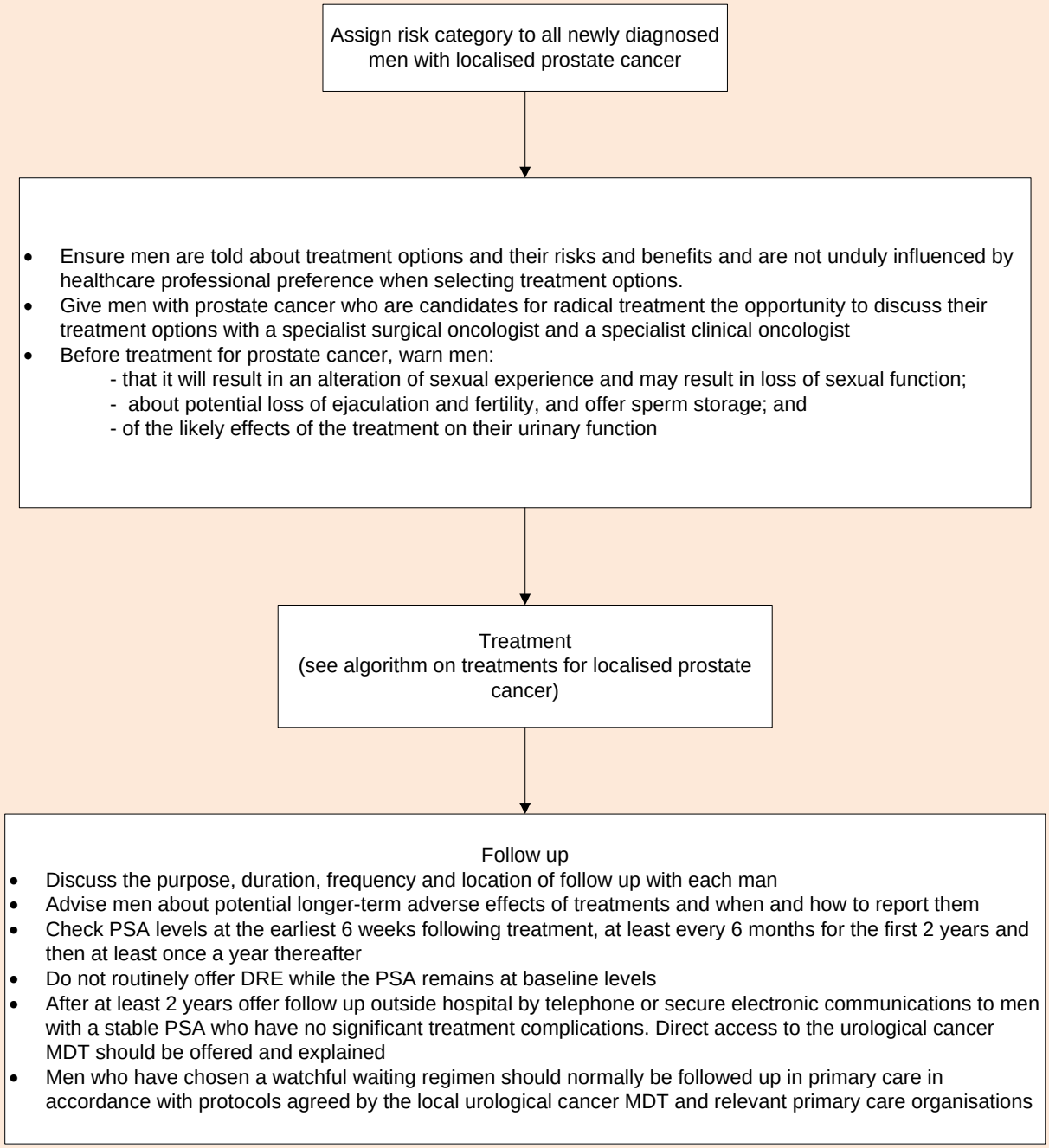
Diagnosis and staging



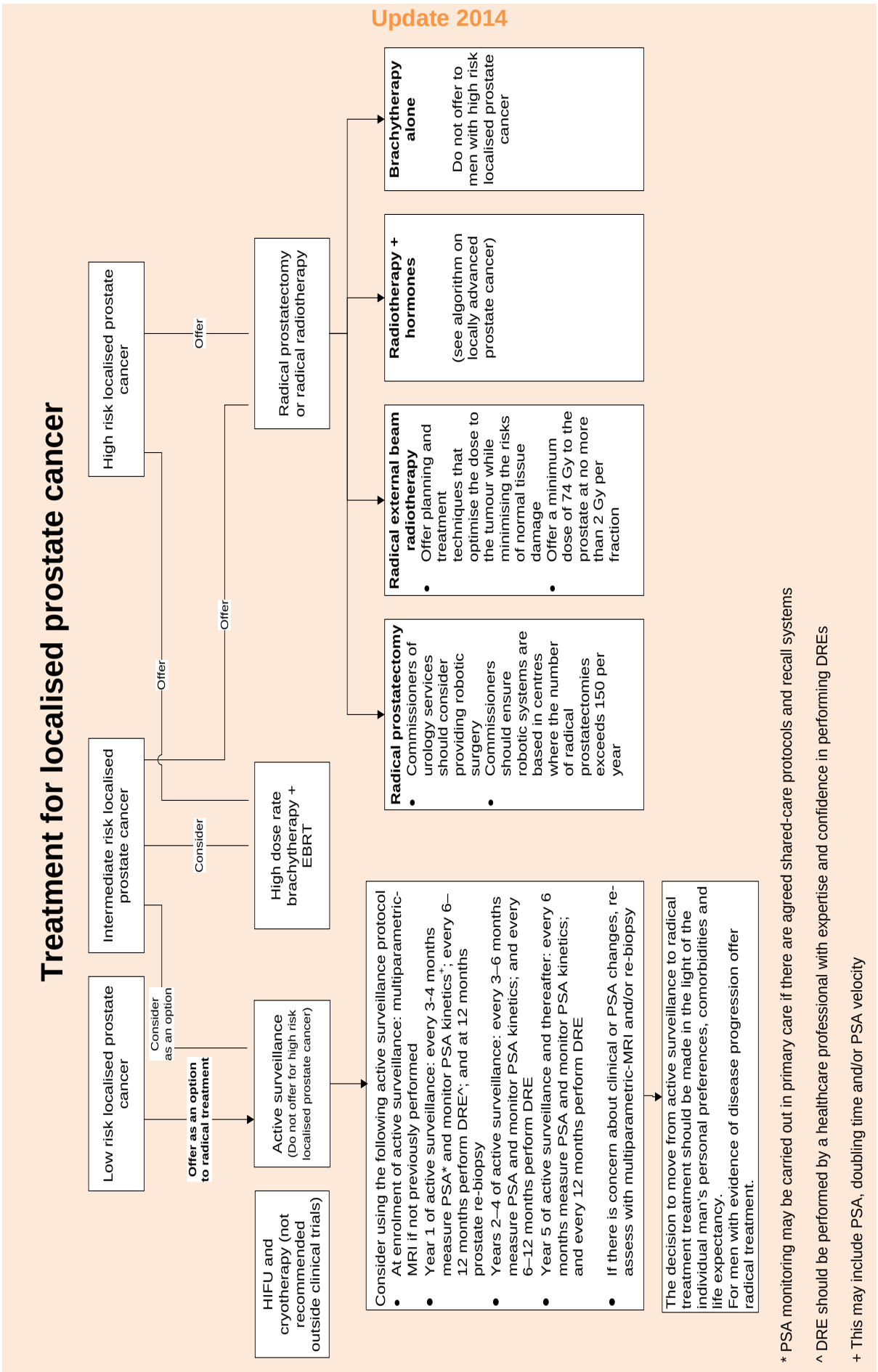
* Undertaking a transrectal ultrasound guided biopsy of the prostate, Prostate Cancer Risk Management Programme, 2006

^ Does not include men on active surveillance

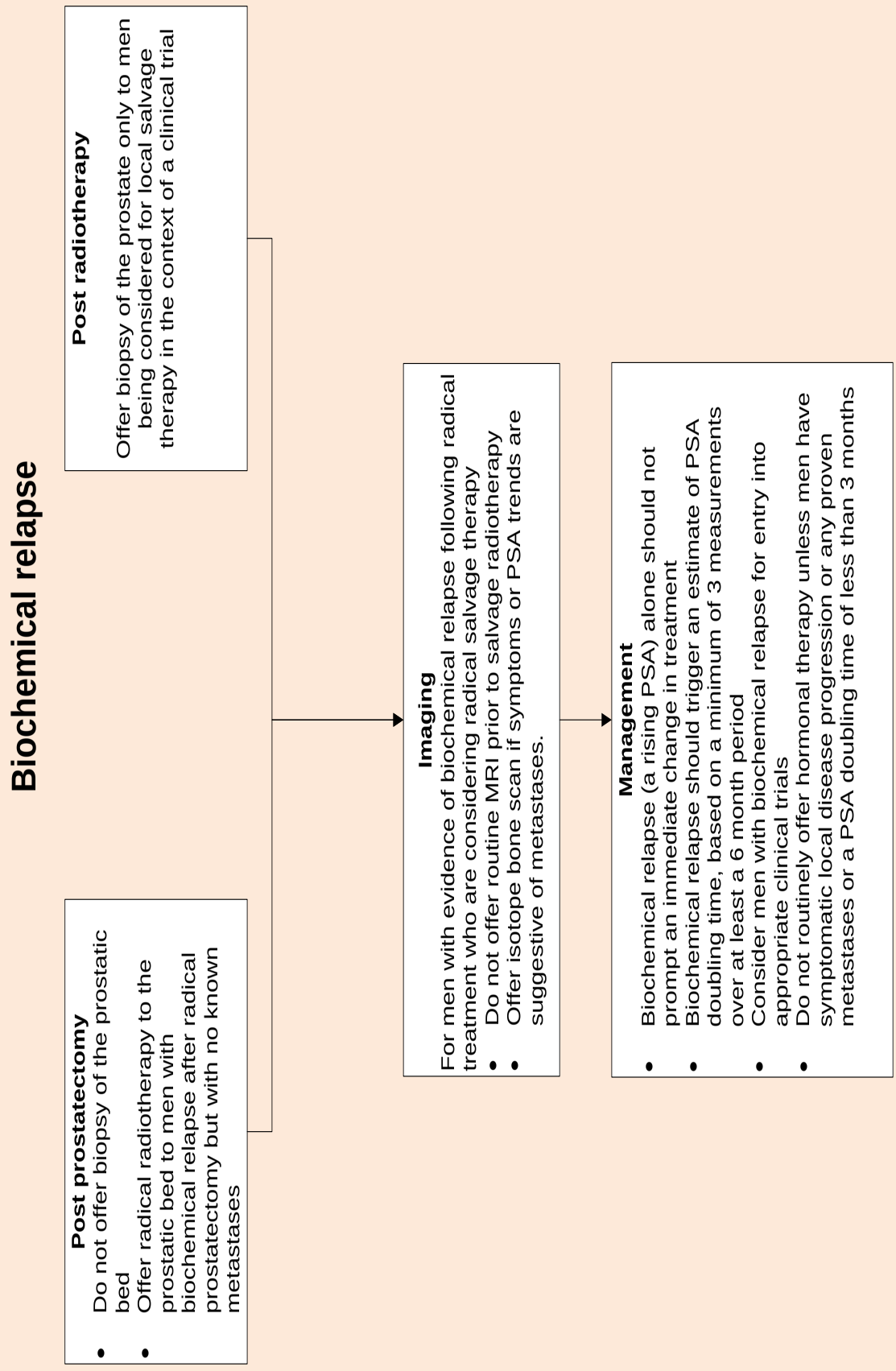
Localised prostate cancer

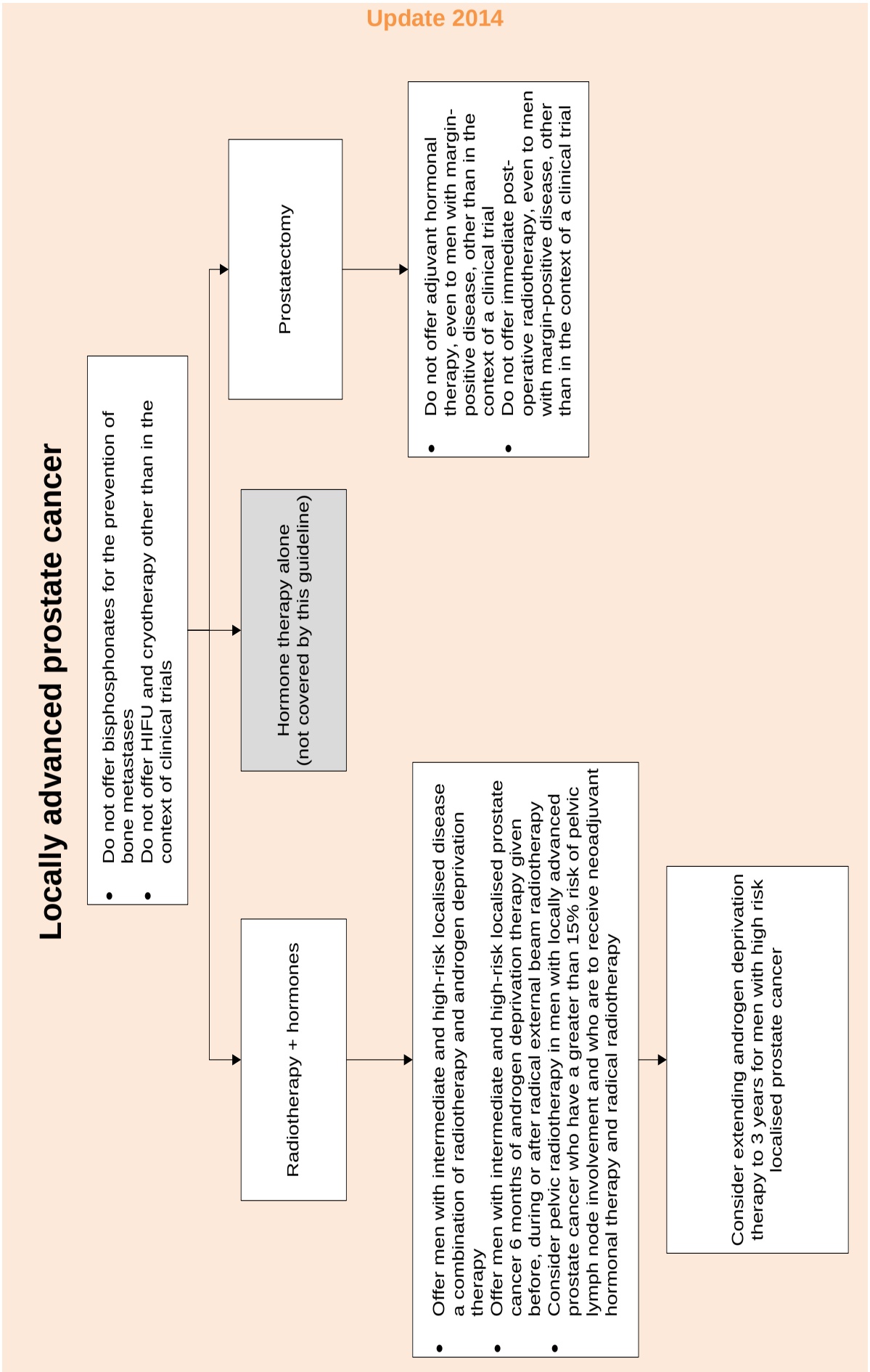


Update 2014

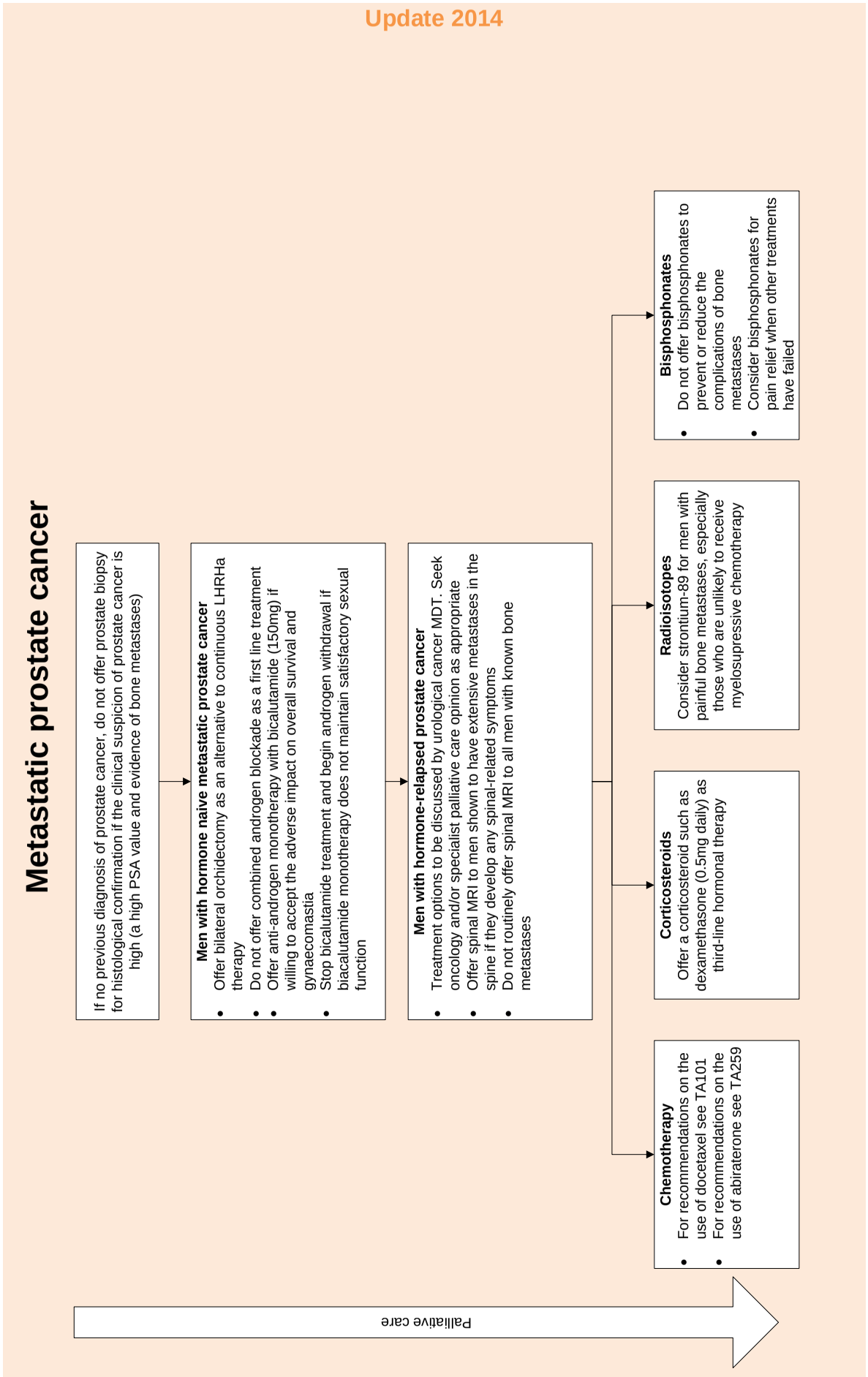


Update 2014

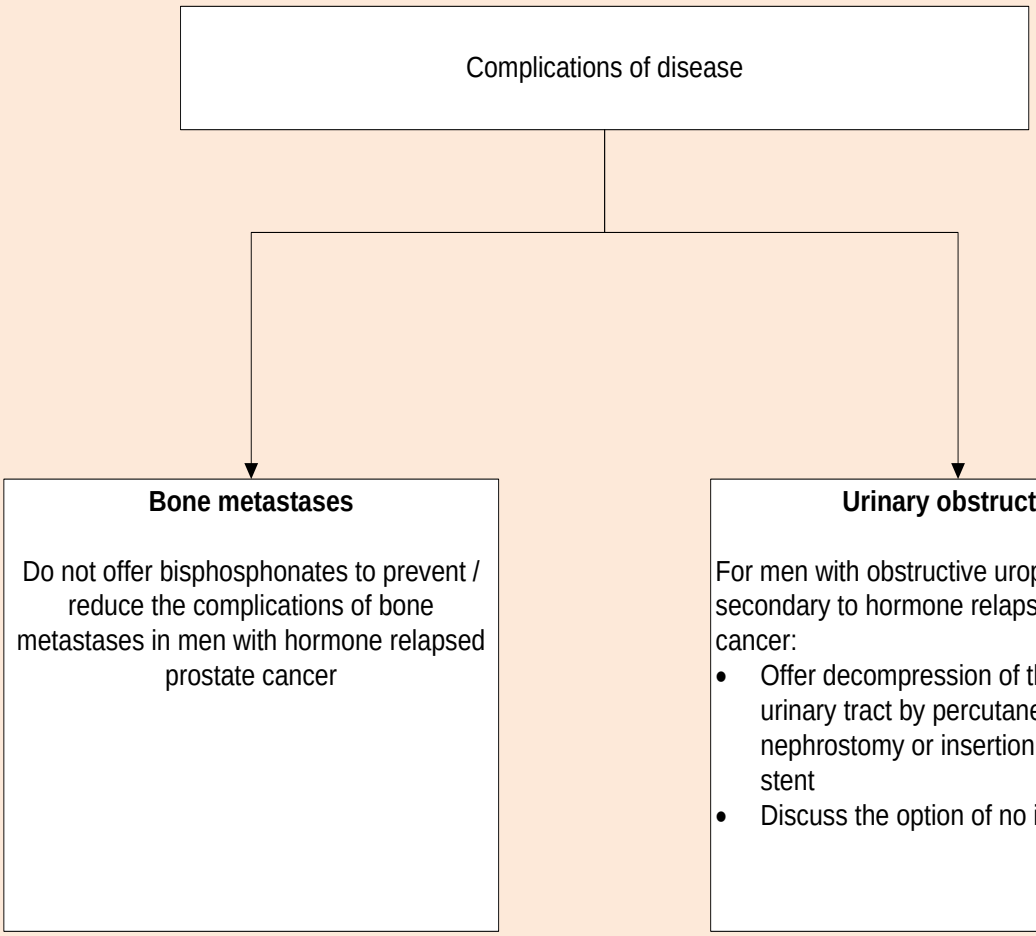




Update 2014



Managing complications of disease



Update 2014

Managing complications of treatment

Urinary symptoms

- Offer men experiencing troublesome urinary symptoms before treatment a urological assessment
- Ensure men with troublesome urinary symptoms after treatment have access to specialist continence services
- Refer men with intractable stress incontinence to a specialist surgeon for consideration of an artificial urinary sphincter
- Do not offer injection of bulking agents into the distal urinary sphincter to treat stress incontinence

Bowel symptoms*

- Ensure men with signs or symptoms of radiation induced enteropathy (RIE) are offered care from a team of professionals with expertise in RIE
- Tell men there is a small increase in the risk of colorectal cancer after radical external beam radiotherapy for prostate cancer
- Carry out full investigations, including flexible sigmoidoscopy, in men who have symptoms of RIE to exclude inflammatory bowel disease for malignancy of the large bowel and to ascertain the nature of the radiation injury

Sexual dysfunction

- Ensure men have early and ongoing access to specialist erectile dysfunction services
- Offer phosphodiesterase type 5 (PDE5) inhibitors to men who experience loss of erectile function
- If PDE5 inhibitors fail to restore erectile function or are contraindicated, offer a choice of intraurethral inserts, penile injections, penile prosthesis, vacuum devises

Endocrine

Hot flushes

- Offer medroxyprogesterone (20mg a day), initially for 10 weeks. Evaluate the effect at the end of the treatment
- Consider cyproterone acetate or megestrol acetate (20mg twice a day for four weeks) if medroxyprogesterone is not effective or not tolerated
- Tell men there is no good quality evidence for the use of complimentary therapies

Gynaecomastia

- Offer men starting long term bicalutamide monotherapy (>6 months) prophylactic radiotherapy to both breast buds within the first month of treatment. Choose a single fraction of 8 Gy using orthovoltage or electron beam radiotherapy.
- Consider tamoxifen if radiotherapy is unsuccessful in preventing gynaecomastia

Fatigue

- Tell men who are starting androgen deprivation therapy that fatigue is a recognised side effect of this treatment
- Offer men who are having androgen deprivation therapy supervised resistance and aerobic exercise at least twice a week for 12 weeks to reduce fatigue

Osteoporosis

Preventing osteoporosis

For men having androgen deprivation therapy

- Consider assessing fracture risk in line with Osteoporosis Fragility Fracture Risk (NICE clinical guideline 146)
- Do not routinely offer bisphophonates to prevent osteoporosis

Managing osteoporosis

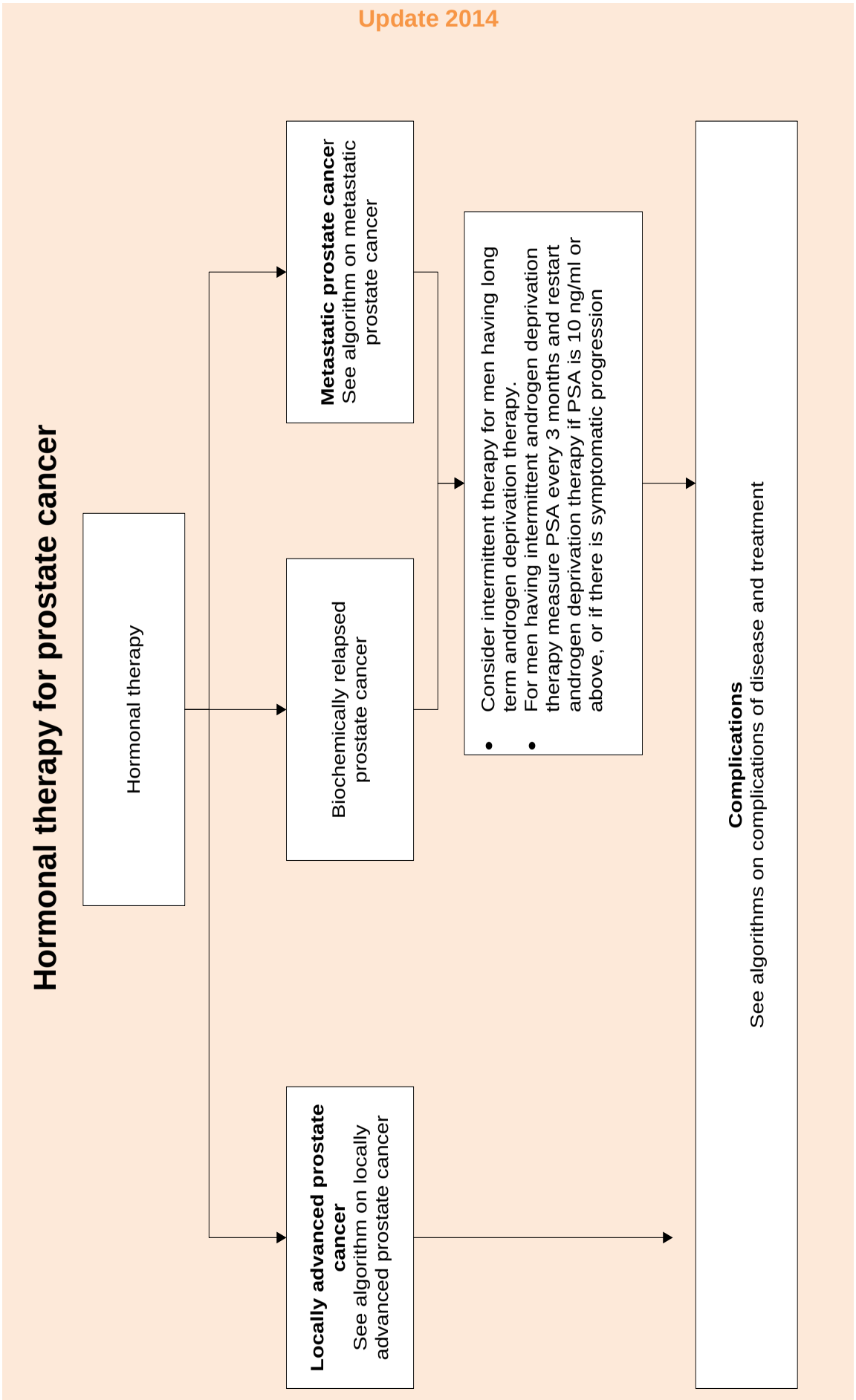
For men having androgen deprivation therapy

- Offer bisphosphonates
- Consider denosumab if bisphosphonates are contraindicated or not tolerated

Update 2014

* The nature and treatment of radiation –induced enteropathy should be included in the training programmes for oncologists and gastroenterologists

Update 2014



1 Epidemiology

1.1 Introduction

1.1.1 Risk Factors

Age is one of the strongest risk factors for prostate cancer, with around 85% of all cases diagnosed in those aged over 65 years and an estimated incidence of only 0.1% in those aged under 50 years (Patel and Klein 2009). Family history has been shown to be a risk factor for prostate cancer; approximately 5-10% of cases are thought to have a substantial inherited component. It has been established that strong predisposing genes could be responsible for up to 40% of cases in younger men up to the age of 55 (Elo and Visakorpi 2001; Carter *et al*. 1992). For example, a recurrent mutation (G84E) in the HOXB13 gene has recently shown to be significantly associated with an increased risk of prostate cancer and is significantly more common in men with early-onset, familial disease. The relative risk to a patient increases with increasing numbers of first-degree relatives diagnosed and the father-to-son relative risk is increased 2.5-fold whilst the relative risk between brothers is increased 3.4-fold (Johns and Houlston 2003). Patients with hereditary prostate cancer are often diagnosed 6-7 years prior to spontaneous cases (Bratt 2002). A link between prostate cancer and a family history of breast cancer has also been established, believed to be due to the BRCA1 and BRCA2 genes (Thompson and Easton 2002; Edwards *et al*. 2003).

Ethnicity has been shown to be a risk factor for prostate cancer (see section 1.1.2.5). The lowest incidence rates of prostate cancer are observed in Asian men, particularly in India, China and Japan. South Asian men living in England have a lower incidence of prostate cancer than their white counterparts (relative risk of 0.8) (Metcalfe *et al*. 2008). Higher rates are seen in Black men; African-American men are thought to have 1.3-2.0 times the risk of developing prostate cancer than Caucasian men, and black men (irrespective of black-African or black-Caribbean origin) have been shown to have a 3-times higher risk of developing prostate cancer than white men (Ben-Shlomo 2008).

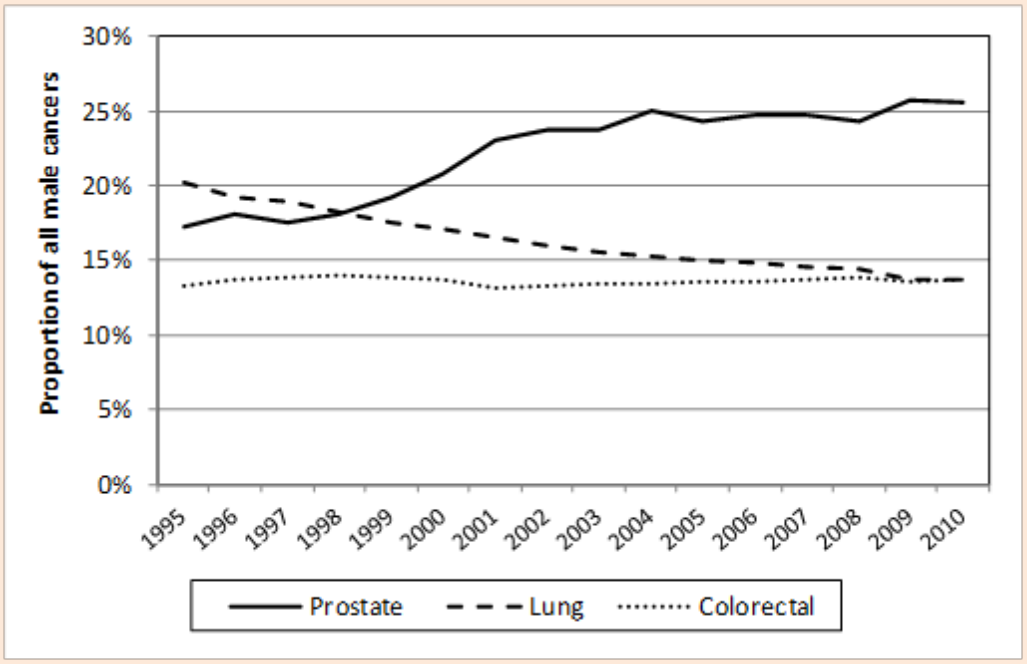
Update 2014

However, studies suggest a change in risk in men moving from Japan to areas such as the US, indicating that exogenous factors may also affect the risk of progression from latent to clinical prostate cancer (Zaridze *et al*. 1984). There is inconclusive evidence on the influence of factors such as food consumption, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, and occupational exposure on the development of prostate cancer (Kolonel *et al*. 2004). Obesity has also been linked to prostate cancer, with an association between high-grade disease and increasing body mass index (BMI) (Rohrmann *et al*. 2003).

1.1.2 Incidence and prevalence

Prostate cancer is now the most common cancer in men in the UK and made up 26% of all male cancers in England and Wales in 2010 (see Figure 1). Prior to 1994 there was a steady rise in the rate of prostate cancer diagnoses which is attributed to the increasing use of transurethral resection of the prostate (TURP) as a treatment of benign prostate hyperplasia (Brewster *et al*. 2000; Evans *et al*. 2003). Improved recording of the diagnosis due to improved registration practice may also have contributed to this increase. Following this the rate of diagnoses was relatively stable until 1998 which may reflect the rising number of diagnoses due to increased prostate specific antigen (PSA) testing but a falling number resulting from the performance of TURPs (Evans *et al*. 2003). The following rapid increase from 1998 until 2001 is thought to be due to more widespread use of PSA testing (Office for National Statistics 2012). Since 2001 the rate of increase has slowed to around 1,000 new cases in England and Wales each year ($p<0.001$).

Figure 1: Proportion of all malignant male cancers contributed by the three most common cancers in men in England and Wales, 1995-2010 (source: SWPHO, WCISU)*

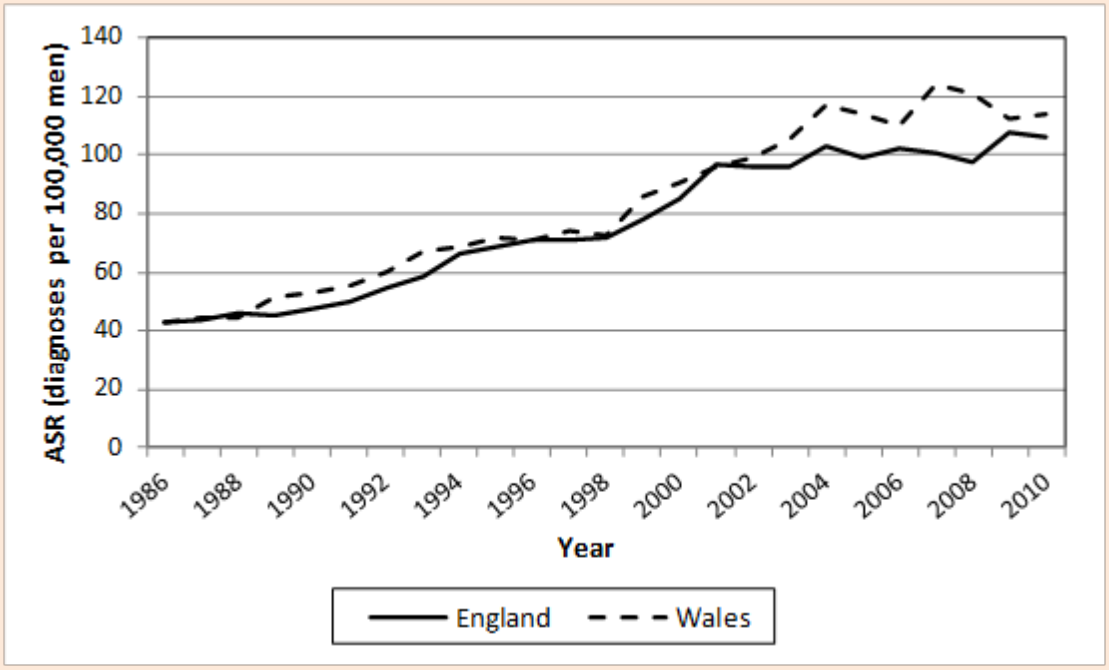


**Excludes non-melanoma skin cancer (ICD10 code C44)*

Figure 2 shows the age-standardised incidence rate of prostate cancer in England and Wales over time. Both England and Wales show a similar trend with steady increases in prostate cancer prior to 1994 and after 1998. This increase in rates slowed from 2001 in England and from 2005 in Wales. Estimates based on 2007 data suggest prostate cancer will stabilise and continue to make up 26% of all male cancers in 2030 (Mistry *et al*. 2011). However, this was based on an estimated annual increase of 0.3% in the age-standardised rate. In contrast, the age-standardised rate has shown an annual increase of 2.0% between 2007 and 2010 in England.

Update 2014

Figure 2: Age standardised rate (ASR) of prostate cancer incidence in England and Wales (to European standard population), 1986-2010 (source: SWPHO, WCISU)



Incidence of prostate cancer has increased worldwide since the 1960s due to improved diagnosis and an aging population. Substantial increases were reported in most countries during the 1980s, with the exception of Denmark, Ecuador and Japan (Quinn and Babb 2002). Rates in the USA reached a peak in 1992, prior to this they were more than twice that seen in Sweden and Australia, over three times that seen in the UK, and ten times the levels in countries such as Singapore, Japan, India and China (Quinn and Babb 2002).

Bray *et al*. 2010 report an increasing trend in all of 24 European countries studied. The rate of increase ranged from 3-4% on average per annum since 1990 in The Netherlands, Slovakia, Switzerland and the UK to 6-7% or more in eight countries including France, Germany, Latvia, Spain and the Russian Federation. The highest incidence rates were in Finland, Sweden and The Netherlands, though rates were seen to either stabilise or decrease after 2005.

1.1.27 Incidence by Cancer Network[a]

Figure 3 shows the variation in incidence of prostate cancer across the Cancer Networks in England and Wales for the time period 2008 to 2010. Each rate is standardised to the European standard population to take into account differences in the structure of the populations. During 2008 to 2010, the incidence rate was lowest in the North of England and highest in North Wales (89 and 129 cases per 100,000 population respectively). Variations in rates are likely to reflect regional differences in PSA testing resulting from differences in local policy or public demand.

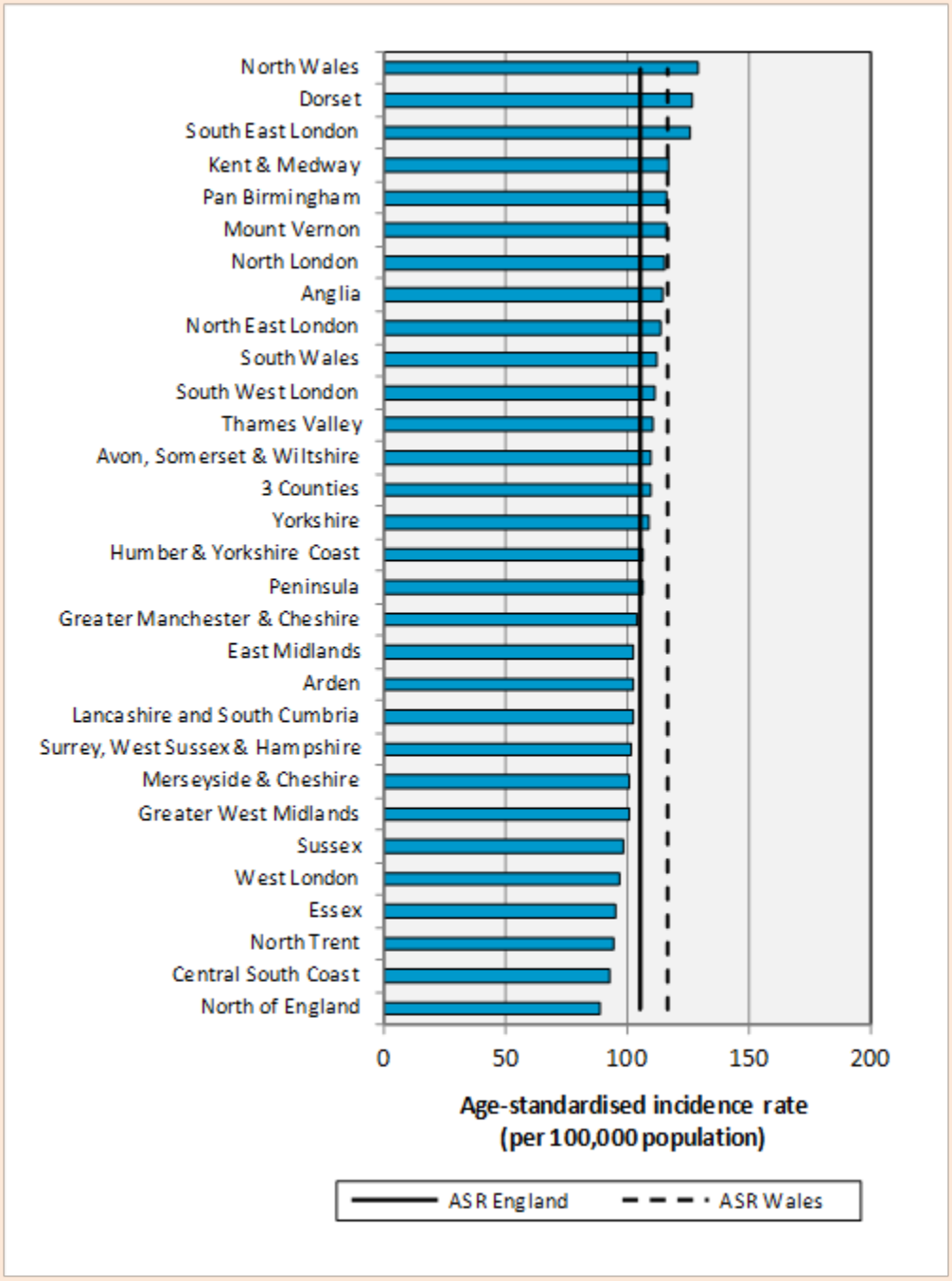
Twenty-two (73%) Cancer Networks showed an increase in rate of between 0.3% (in Lancashire and South Cumbria) and 44.1% (in Mount Vernon) since 2002-2004 (the beginning of a period of stability). The incidence rate in the remaining eight (27%) Cancer Networks decreased by between 0.5% (in the North of England) and 14.1% (in the Central South Coast). The ASRs for England and Wales showed an increase of 5.8% and 8.2% respectively. This compares to the increase of between 2.0% and 42.1% that was seen in all

Update 2014

a Cancer Networks became part of Strategic Clinical Networks, serving larger populations, in April 2013.

Cancer Networks between the years 1996-1998 and 1999-2001. The ASRs for England and Wales increased by 20.3% and 24.8% during this time period respectively.

Figure 3: Age standardised rate (ASR) of prostate cancer incidence in England and Wales, by Cancer Network (to European standard population), 2008-2010 (source: SWPHO, WCISU)

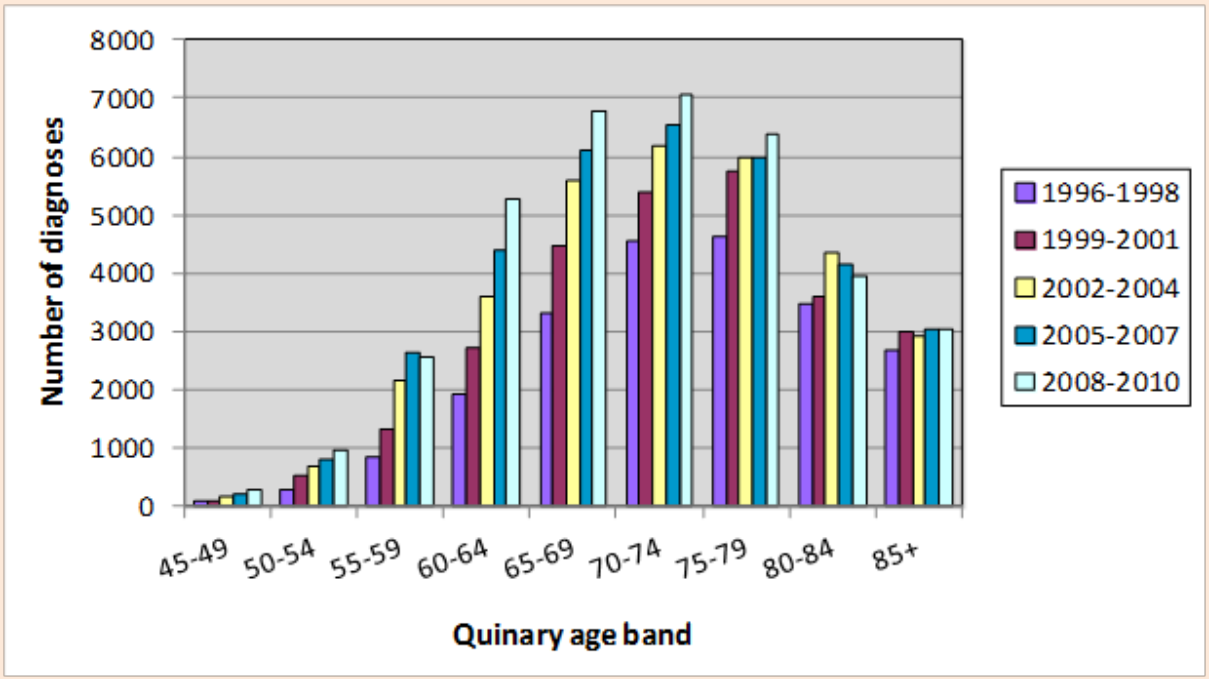


1.1.272 Incidence by age group

The number of diagnoses of prostate cancer in England and Wales is highest among those aged 65 to 79 years (see Figure 4). A rapid increase in the number of diagnoses is seen among those aged 45 to 59 years. This then tapers off and begins to decrease among those in older age groups. This decline has begun earlier, among those aged 75-79 years, since 2002 and a more rapid increase seen between those aged 50-54 and 60-64 years than previously.

Update 2014

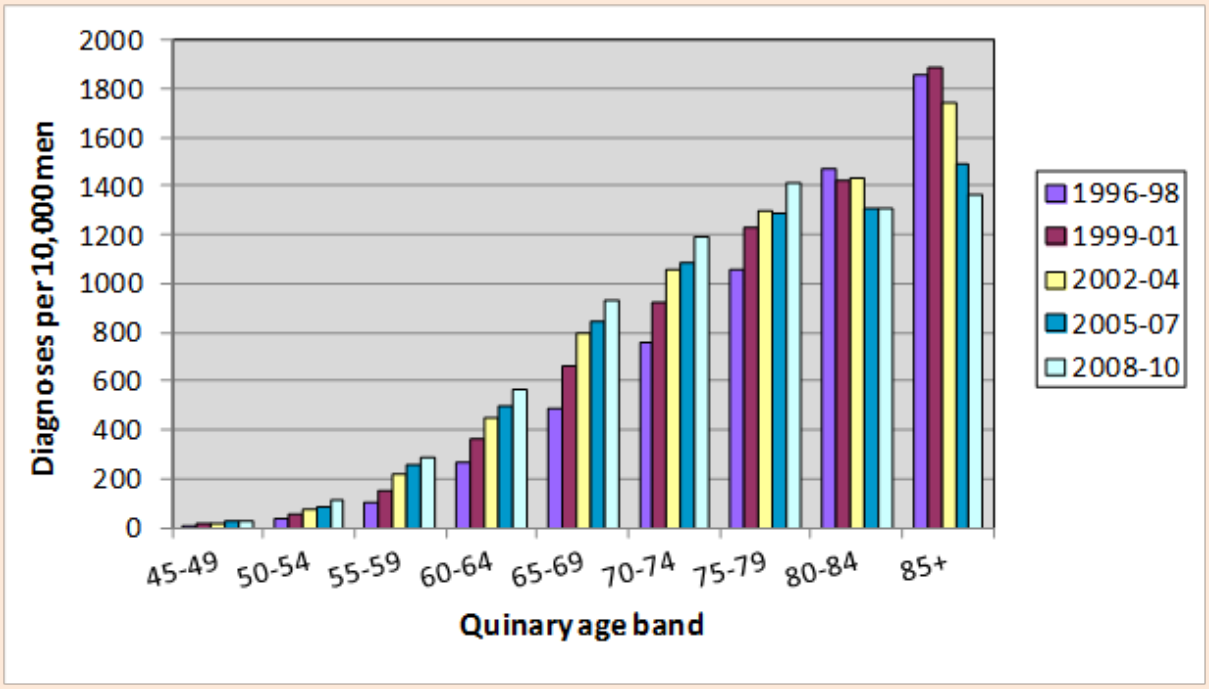
Figure 4: Mean number of prostate cancer diagnoses by 5-year age band, 1996-2010 (source: SWPHO, WCISU)



Update 2014

However, when the population size of these age groups is taken into account, the rate of prostate cancer diagnoses can be seen to increase steadily with age (see Figure 5). From the age of 50 years, the risk of being diagnosed with prostate cancer increases steadily in men, reaching a rate of around 2% of all men in England and Wales in those aged 85 years and over. This trend is seen across four previous time periods: 1996-98, 1999-01, 2002-04 and 2005-09, however, in 2008-10 rates were lower in those aged over 80 years compared to those aged 70-79 years. The largest increase in incidence from one age group to the next is between 45-49 years and 50-54 years for all time periods (> 300% increase). The smallest percentage increase was seen between 80-84 years and 85+ years during 1996-98, but between 75-79 years and 80-84 years during later time periods. This may reflect the increased uptake of PSA testing and subsequent higher chance of diagnosis in the younger age groups. The younger age bands (< 80 years) show a trend for increasing rates of diagnoses in recent years, while the older age bands (80+ years) show a trend for decreasing rates of diagnoses in recent years.

Figure 5: Rate of prostate cancer diagnoses by 5-year age band, 1996-2010 (source: SWPHO, WCISU)



Update 2014

1.1.243 Incidence by cancer grade and stage at diagnosis

The proportion of prostate cancer diagnoses with a Gleason score ≤ 6 has continued to steadily decline over the last 10 years (see Figures 6 and 7). This is primarily due to increasingly rare occurrence of a Gleason score ≤ 5 at diagnosis (1.5% of all known Gleason scores at diagnosis in 2009). It is thought to be the result of a shift in pathological reporting practice and general agreement that the lowest Gleason grade that can be assessed at needle biopsy is a growth pattern of 3. This suggests that a Gleason score of 6 is the lowest possible on peripheral zone needle biopsy (University of Liverpool 2003; Epstein 2000).

The proportion of patients with a Gleason score of 7 at diagnosis continued to steadily increase from 17% in 1996 to 39% in 2009. This again reflects the shift in pathological reporting. The proportion of patients with a Gleason score ≥ 8 has remained relatively stable over the last 10 years, varying between 22% and 27% of all diagnoses where the Gleason score is known. Since 2000, the proportion of diagnoses where the Gleason score is unknown has ranged between 27% and 37%.

Figure 6: Proportion of new cases of prostate cancer by Gleason score at diagnosis, where known, 2000-2009 (source: SWPHO, WCISU)

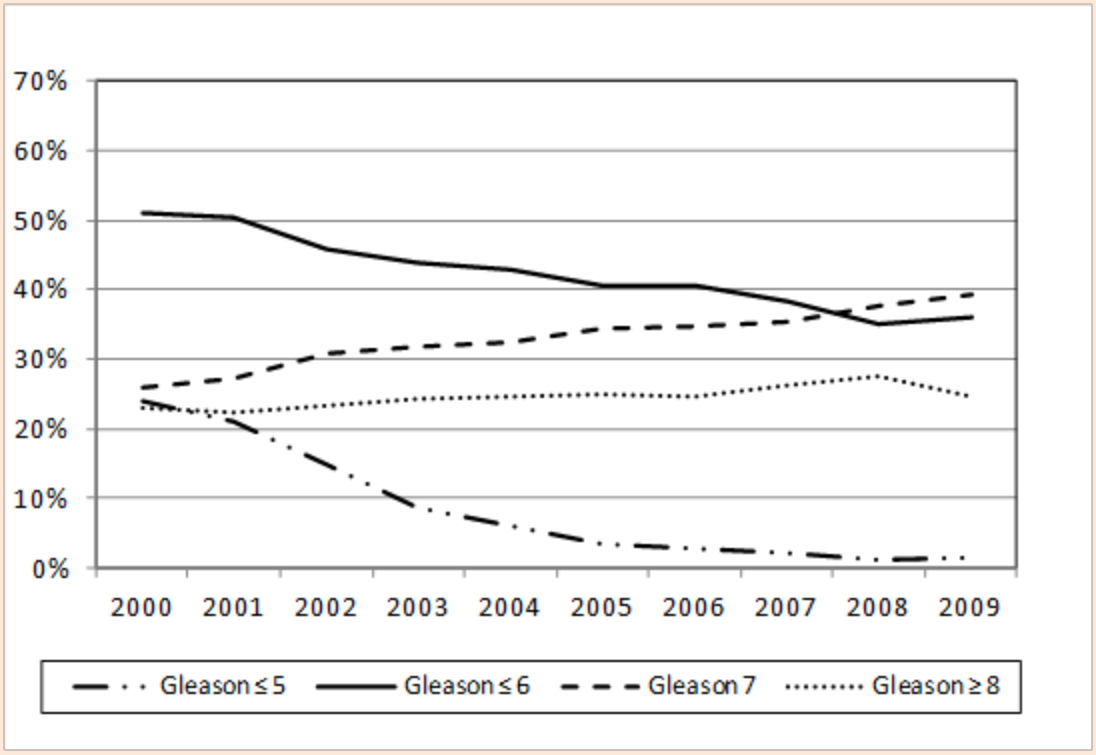
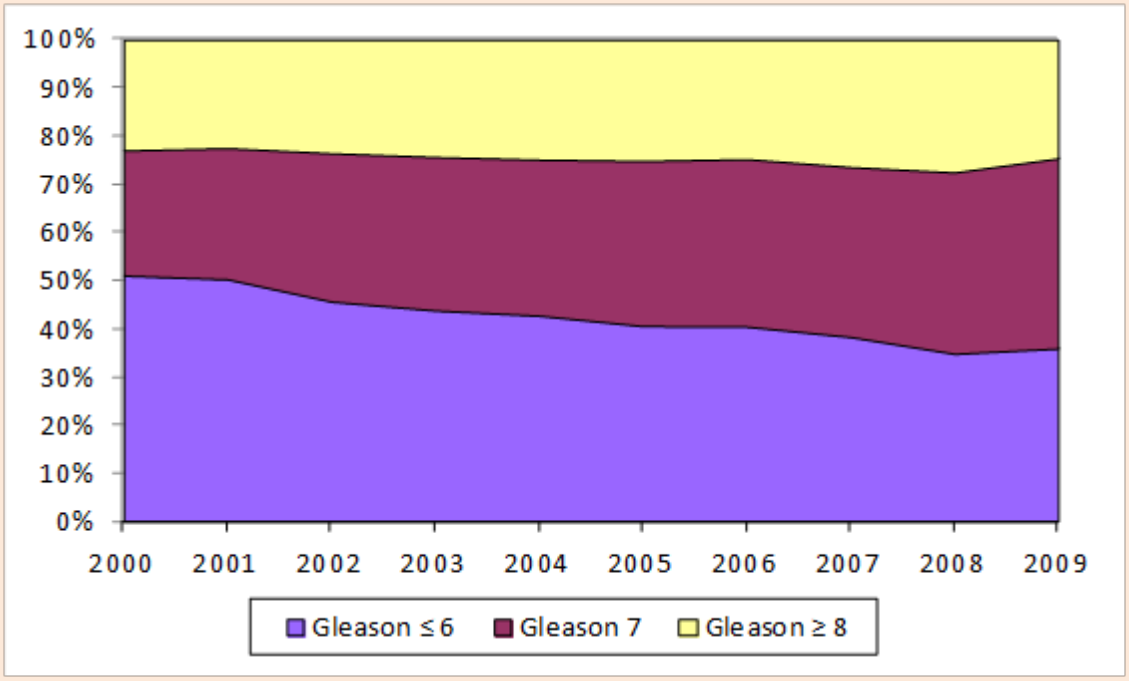


Figure 7: Proportion of new cases of prostate cancer by Gleason score at diagnosis, where known, 2000-2009 (source: SWPHO, WCISU)

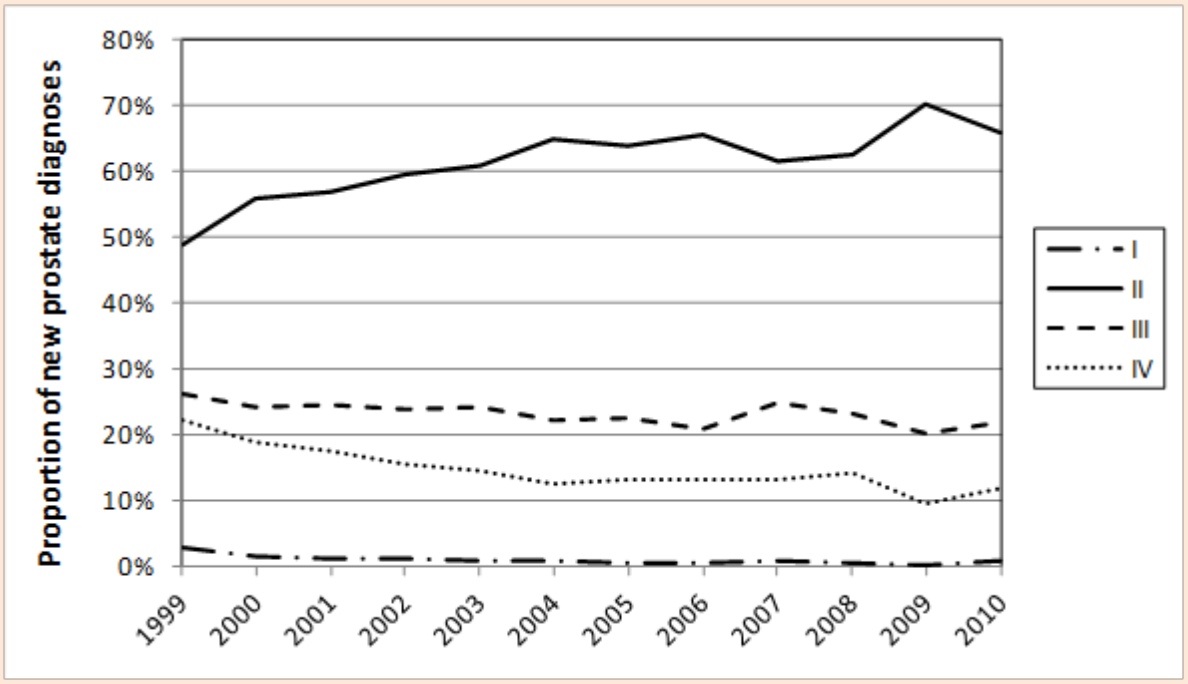


The British Association of Urological Surgeons (BAUS) collects information on the stage at diagnosis through the newly diagnosed registry of urological cancers. However, reporting is voluntary and has decreased substantially in recent years (Bristish Association of Urological Surgeons 2012). The proportion of diagnoses reported through this registry whose stage is unknown has also increased from 19% in 1999 to 48% in 2010. Figure 8 should therefore be treated with caution.

Update 2014

Figure 8 shows an increase in patients diagnosed with prostate cancer stage II over the last 10 years, reaching 66% of diagnoses where stage is known in 2010. Diagnoses of stage IV have declined from 22% in 1999 to 12% in 2010. Diagnoses of stages I and III have remained relatively constant ranging between 0.2% and 1.2%, and 20.1% and 24.7% over the last 10 years respectively.

Figure 8: Proportion of new cases of prostate cancer by stage at diagnosis, where known, 1999-2010 (source: BAUS)

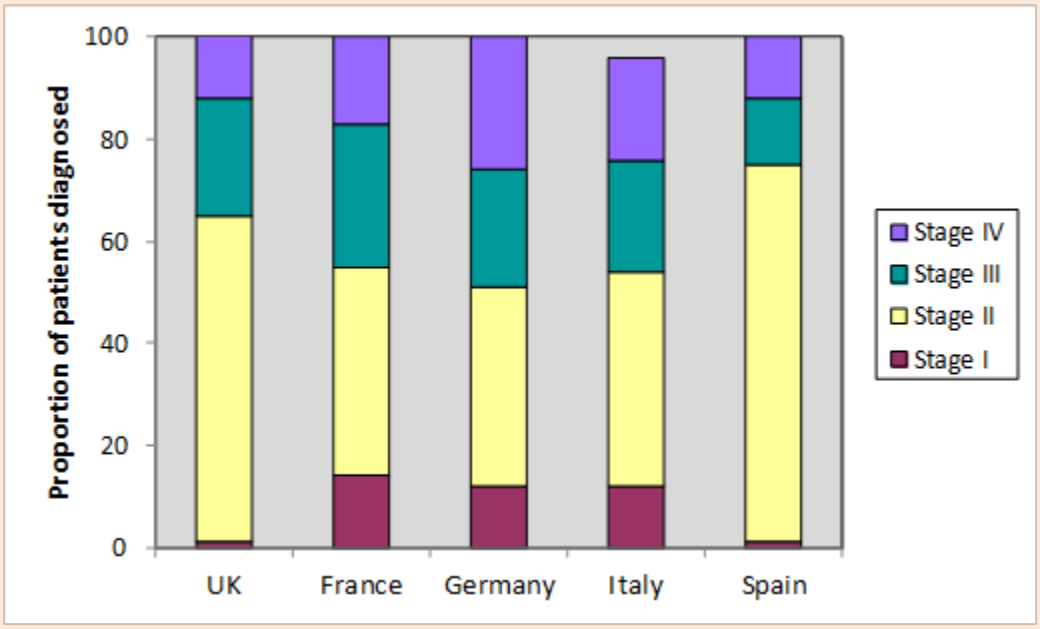


Stages are defined using the full TNM classification of malignant tumours procedure advocated by the IUCC: stage I = T1-T2a N0; stage II = T2b-T2c N0; stage III = T3 N0; stage IV = T4 N0 or any T & N1 or any T, any N & M1

Fourcade *et al*. 2009 compared the proportion of patients with known stage at diagnosis in 2005 from databases in several European countries (see Figure 9). The proportion of patients diagnosed with stage I was higher in France, Germany and Italy (12-14%) than that seen in the UK or Spain (1%). This was predominantly due to a greater proportion of patients being diagnosed as stage II in the latter two countries (64% and 74% respectively compared to 39-42%). The proportion of patients diagnosed at stage III ranged from 13% to 28%, being lowest in Spain and highest in France. The proportion of patients diagnosed at stage IV was lowest in Spain and the UK (12% and 13% respectively compared to 17-26%) and highest in Germany. However, stage at diagnosis was unknown for varying proportions of patients and reporting was not mandatory for all databases used. Results should therefore be interpreted with caution.

Update 2014

Figure 9: Proportion of new cases of prostate cancer by stage at diagnosis and country, where stage is known, 2001-2006 (source: Fourcade *et al*. 2009)



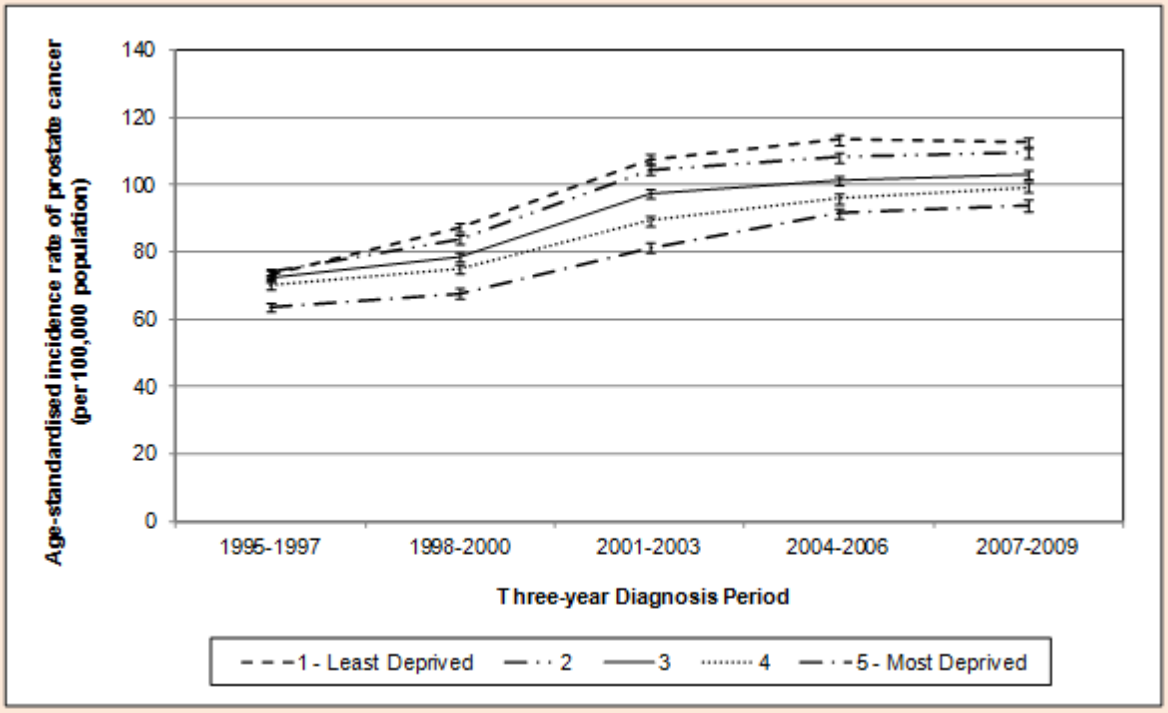
Stages are defined using the full TNM classification of malignant tumours procedure advocated by the IUCC: stage I = T1-T2a N0; stage II = T2b-T2c N0; stage III = T3 N0; stage IV = T4 N0 or any T & N1 or any T, any N & M1. Data estimates taken from different datasets and time periods during 2001-2006

Update 2014

1.1.274 Incidence of prostate cancer by socioeconomic status

Figure 10 shows the age-standardised incidence rate of prostate cancer to vary significantly by income deprivation quintile, decreasing as deprivation increases. These differences in rates between deprivation quintile groups have also increased since 1995-1997, to a gap of 18.9 new cases per 100,000 population between the most and least deprived quintiles in 2007-2009.

Figure 10: Age-standardised incidence rate of prostate cancer (per 100,000 population) for 3-year cohorts by income quintile domain, 1995-2009 (source: NCIN)



Studies have also found more deprived patients to be significantly more likely to have an advanced stage at diagnosis. With those in the most deprived quintile estimated to have an odds ratio of an advanced stage at diagnosis of 1.37 (95% CI 1.23-1.52) compared to those who were considered affluent (Lyratzopolous *et al*. 2013).

Update 2014

1.1.295 Incidence of prostate cancer by ethnicity

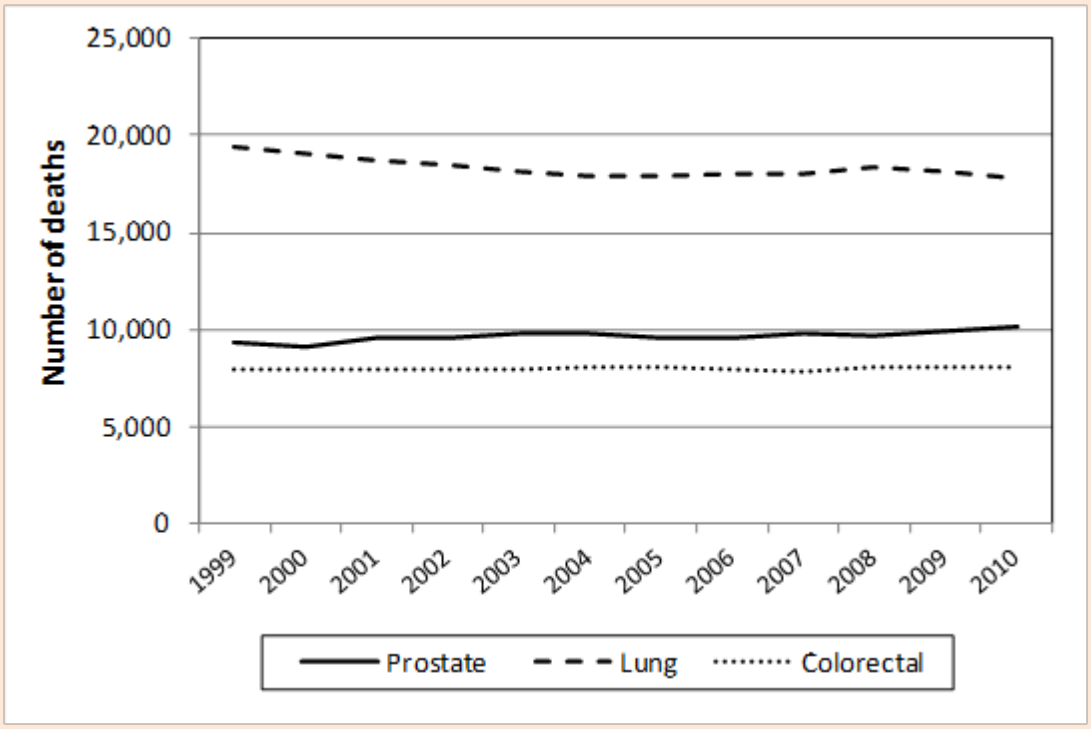
For the years 2002-2006 cancer registration data was linked with Hospital Episode Statistics (HES) to derive information on the ethnicity of prostate cancer patients. However, the availability and accuracy of ethnicity data was limited and the ethnic group of 37% of cases remained unknown. Where known, the ASR were 97 in the White ethnic group, 203 were Black, 49 for Asian, and less than 37 were Chinese, and 80 for mixed ethnicity or other per 100,000 population (National Cancer Intelligence Network 2009).

1.163 Mortality

Prostate cancer is the second most common cause of death due to cancer in men in England and Wales, below only lung cancer (see Figure 11). However, while lung cancer has shown a slow decline in men over the past 30 years, deaths from prostate cancer have remained relatively consistent since 2001 with a slight increase in 2009 and 2010.

These figures only include deaths where prostate cancer is recorded as the underlying cause. However, if deaths where prostate cancer was mentioned on the death certificate were included, the number in England would increase from an average of 8,596 to 11,768 deaths per year during 2001-2010, and from approximately 1.8% to 2.5% of all deaths in England (National End of Life Care Intelligence Network 2012).

Figure 11: Number of deaths in men due to the three most common male cancers in England and Wales, 1999-2010 (source: ONS, WCISU)

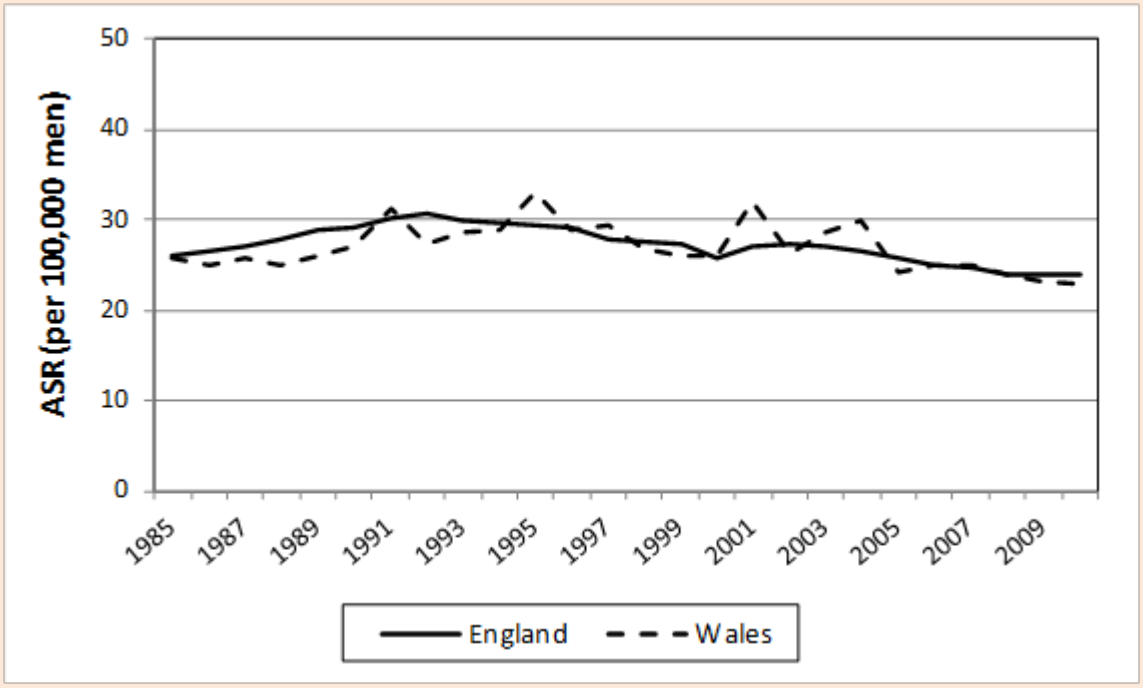


To compensate for changes in the interpretation of the rules on death certification in 2000 the number of deaths due to prostate cancer recorded prior to 2001 have been multiplied by a factor of 1.038 (Office for National Statistics 2002; Office for National Statistics 2003).

Since reaching a peak of 30.7 per 100,000 population in 1992, the age standardised mortality rate for prostate cancer in England has shown a decline to 23.8 per 100,000 population in 2010 (see Figure 12). Despite much greater variability the mortality rate in Wales suggests a similar trend. As the number of deaths remains relatively constant it is likely the declining mortality rate is counteracted by an aging population.

Update 2014

Figure 12: Directly age standardised mortality rate (ASR) from prostate cancer in England and Wales (to European standard population), 1985-2009 (source: ONS, WCISU)



Update 2014

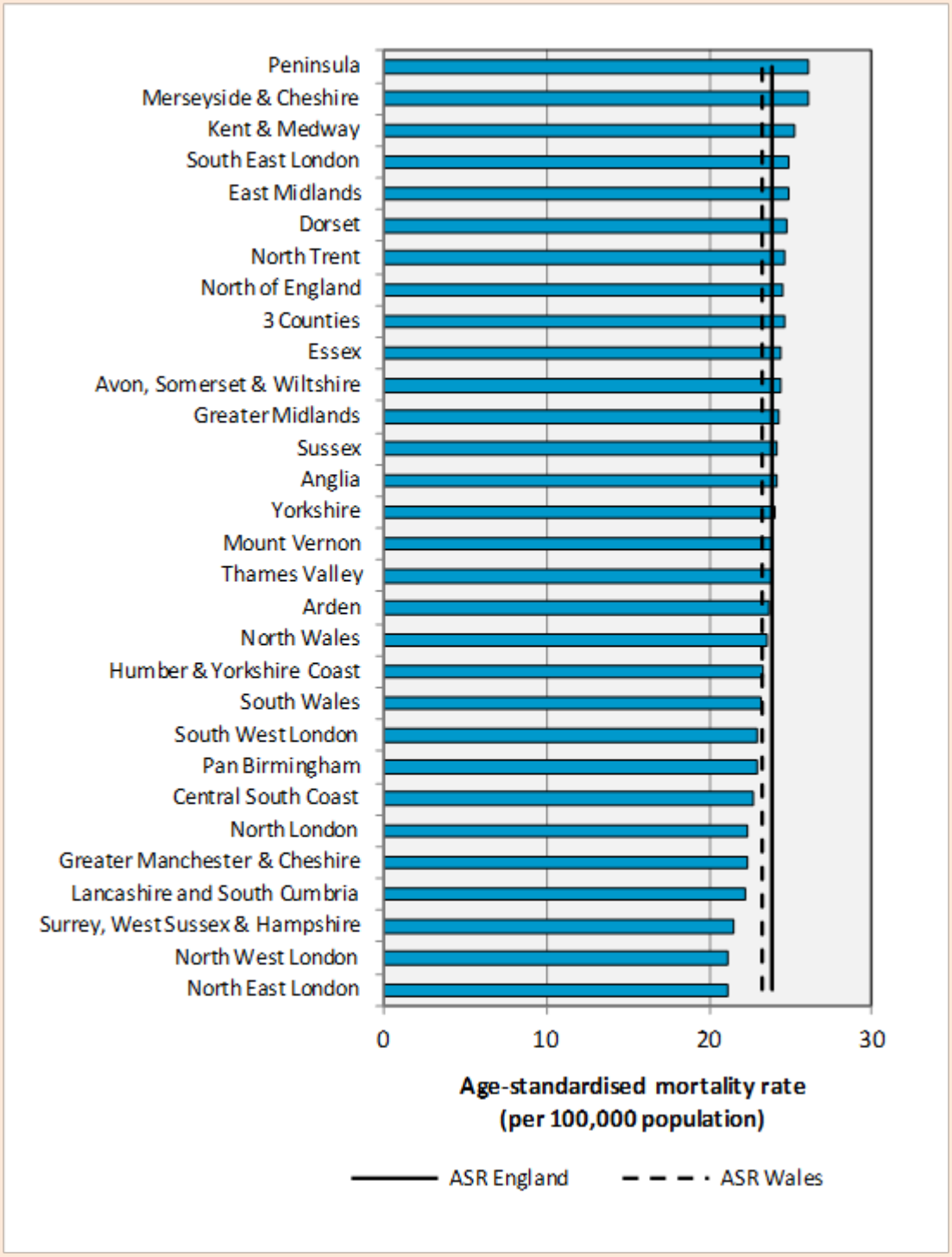
Worldwide mortality rates for prostate cancer have seen an overall decrease since 1990, by about 24% in the US and some Western-European countries including the UK, Austria, France and Germany show annual declines of 2-4% per annum since 1990 (Jemal *et al*. 2009; Bray *et al*. 2010).

1.1.3.1 Prostate cancer mortality by Cancer Network

Figure 13 shows the variation in mortality due to prostate cancer across the Cancer Networks in England and Wales for the time period 2008 to 2010. Each rate is standardised to the European standard population to take into account differences in the structure of the populations. During 2008 to 2010, the mortality rate was lowest in North West London and in North East London (21.1 deaths per 100,000 population in both). It was highest in Merseyside and Cheshire and in Peninsula (26.1 deaths per 100,000 population in both).

All cancer networks showed a decrease in the mortality rate since 2002 to 2004, ranging from a 20.0% decrease in South Wales to a 0.7% decrease in Dorset. The exception to this was in Merseyside and Cheshire which saw no change. The age-standardised mortality rates for England and Wales showed a decrease of 11.5% and 17.7% respectively.

Figure 13: Age standardised rate (ASR) of prostate cancer mortality in England and Wales, by Cancer Network (to European standard population), 2008-2010 (source: ONS, WCISU)



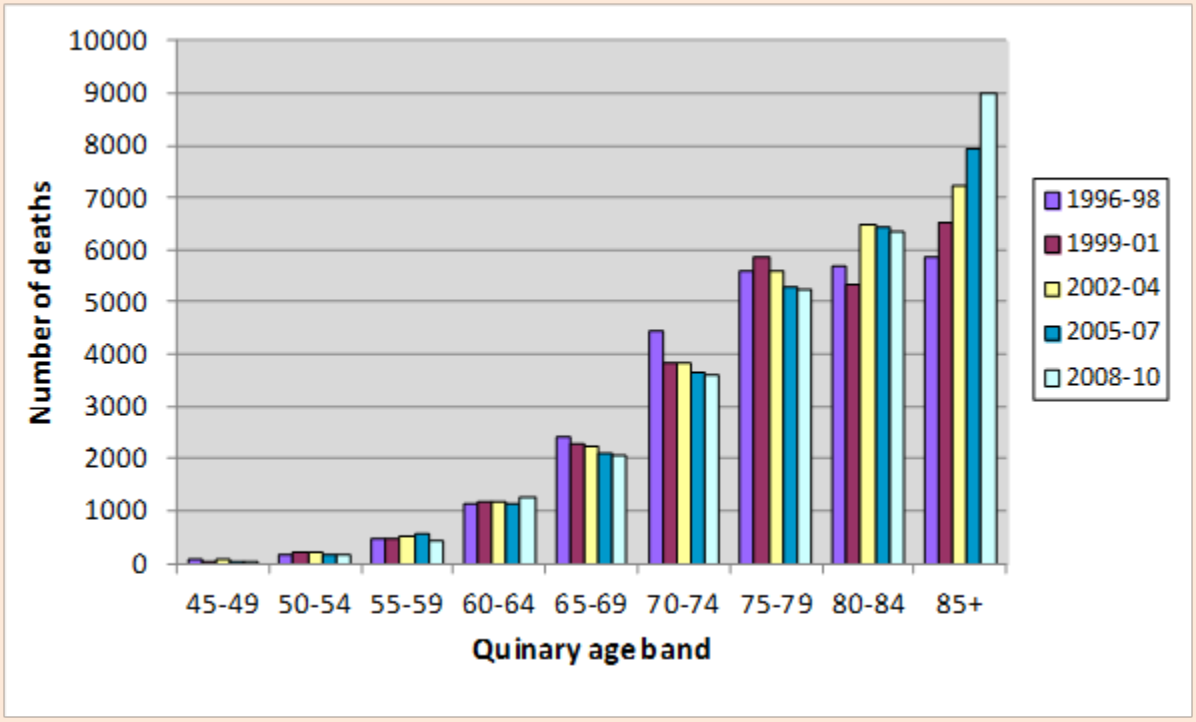
1.1.352 Mortality by age group

During 2001-2010 deaths from prostate cancer made up 0.7% of all deaths in men aged under 65 years, 2.3% in men aged 65-84 years, and 1.5% of all deaths in men aged 85 years and over (National End of Life Care Intelligence Network 2012). The number of deaths due to prostate cancer in England and Wales has increased almost linearly with age in recent years (see Figure 14). In comparison, the time periods 1996-1998 and 1999-2001 show a more rapid increase up to the age of 75-79 years, then a much slower increase. The number of

Update 2014

deaths continues to be highest in those aged 85 years and over and the proportion of all prostate cancer deaths in those aged 85+ years has increased steadily from 23% in 1996-1998 to 32% in 2008-2010.

Figure 14: Mean number of prostate cancer deaths by 5-year age band, 1996-2010 (source: SWPHO, WCISU)

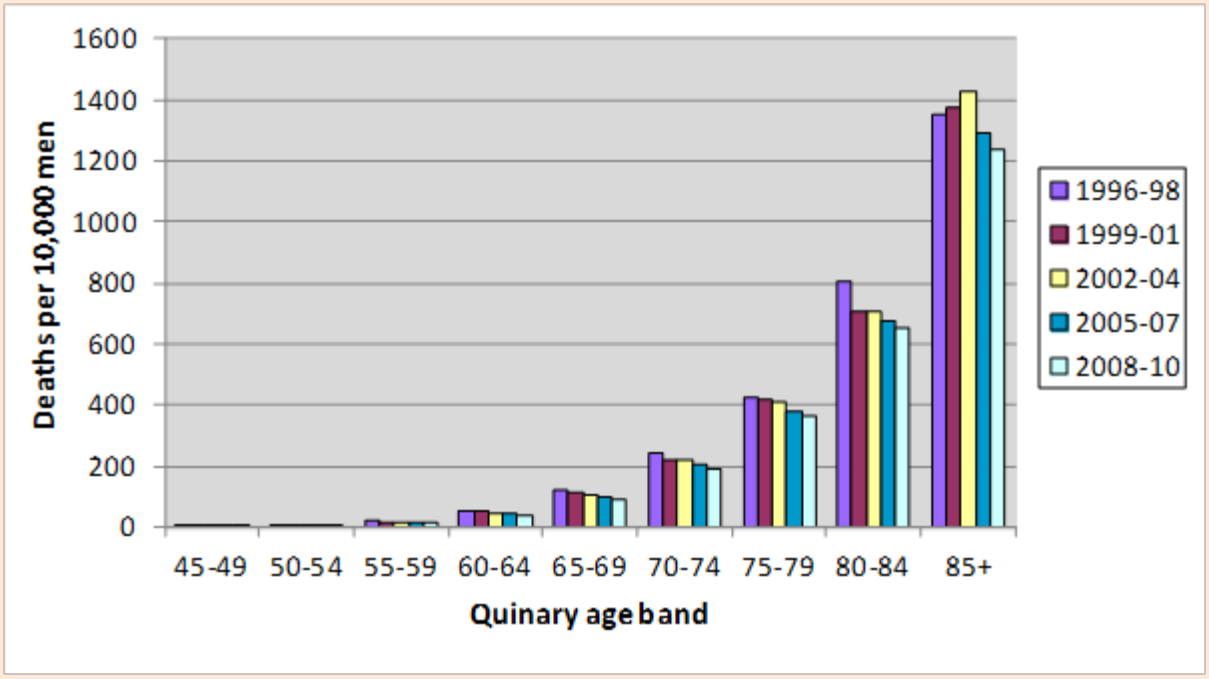


Once the population size of these age groups is taken into account, the mortality rate of prostate cancer can be seen to increase at a slower rate until the age of 60-65 years then follows a rapid increase with age (see Figure 15). This trend can be seen in all time periods from 1996 to 2010. The largest increase in mortality from one age group to the next is between 80-84 years and 85+ years for all time periods. While the smallest percentage increase is seen between 45-49 years and 50-54 years for all time periods. All age groups show a decline in mortality over time, with the exception of those aged 85+ years during 1999-2004.

Many deaths from prostate cancer occur at an advanced stage when the probability of death from other causes is high. Therefore any treatment which delays death may result in an apparent reduction in prostate cancer mortality.

Update 2014

Figure 15: Prostate cancer mortality rate by 5-year age band, 1996-2010 (source: SWPHO, WCISU)

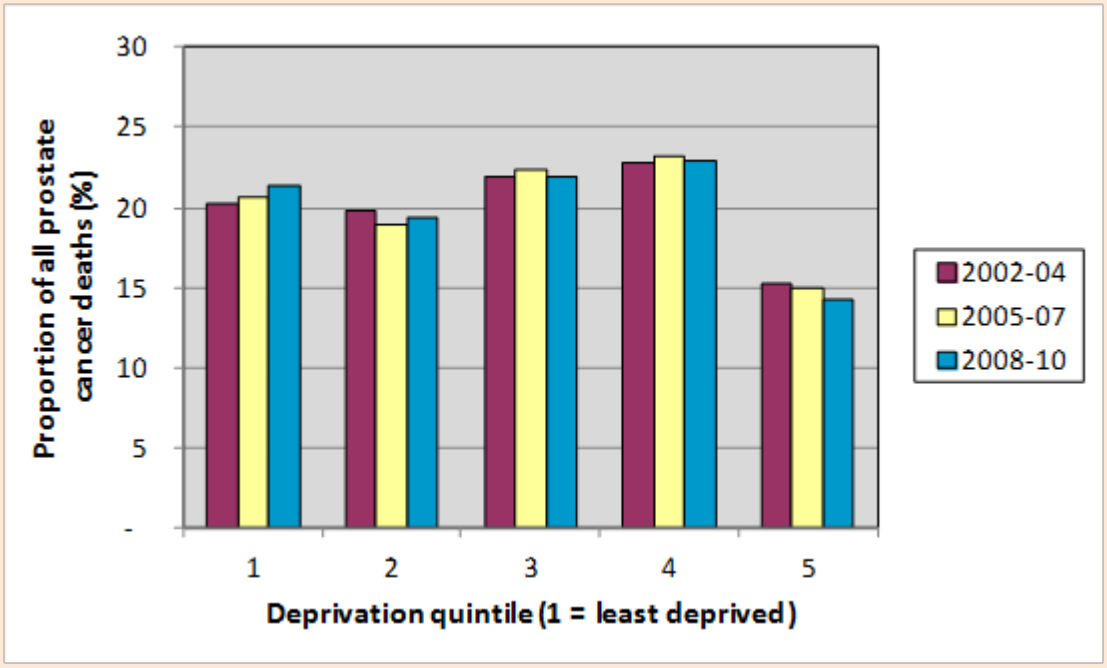


1.1.3.3 Mortality by socioeconomic status

Figure 16 shows the proportion of deaths due to prostate cancer which occurred in each quintile of income deprivation during three time periods. For all time periods, the proportion of deaths is lowest in the most deprived quintile. This may be due to better case ascertainment in more affluent groups of men and a greater likelihood of diagnosis (see section 1.2.1).

Update 2014

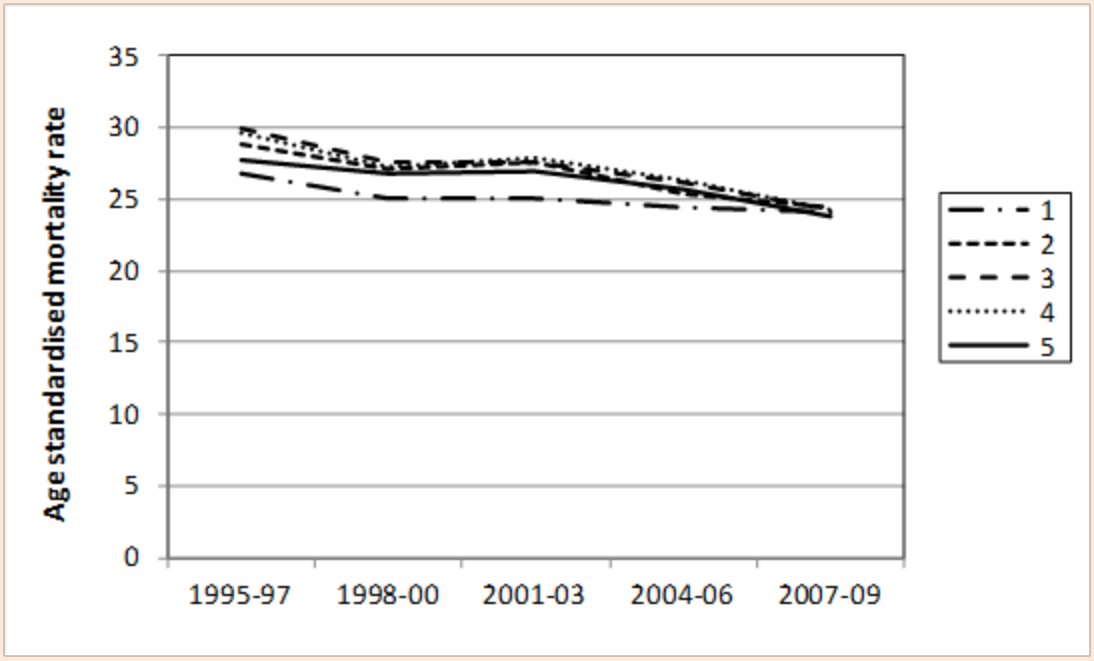
Figure 16: Proportion of deaths due to prostate cancer by quintile of income deprivation, 2002-2010 (source: SWPHO)



The age standardised mortality rate has decreased in all quintiles of income deprivation since 1995-97, with the largest decrease seen in quintile 3. A narrowing of the mortality rates

in the different quintiles has occurred in recent years (see Figure 17). This is due primarily to the mortality rate in the least deprived quintile decreasing at a slower rate. However, no significant association between income deprivation quintile and the mortality rate was found during any of the time periods.

Figure 17: Age standardised mortality rate by quintile of income deprivation, 1995-2009 (source: SWPHO)



Update 2014

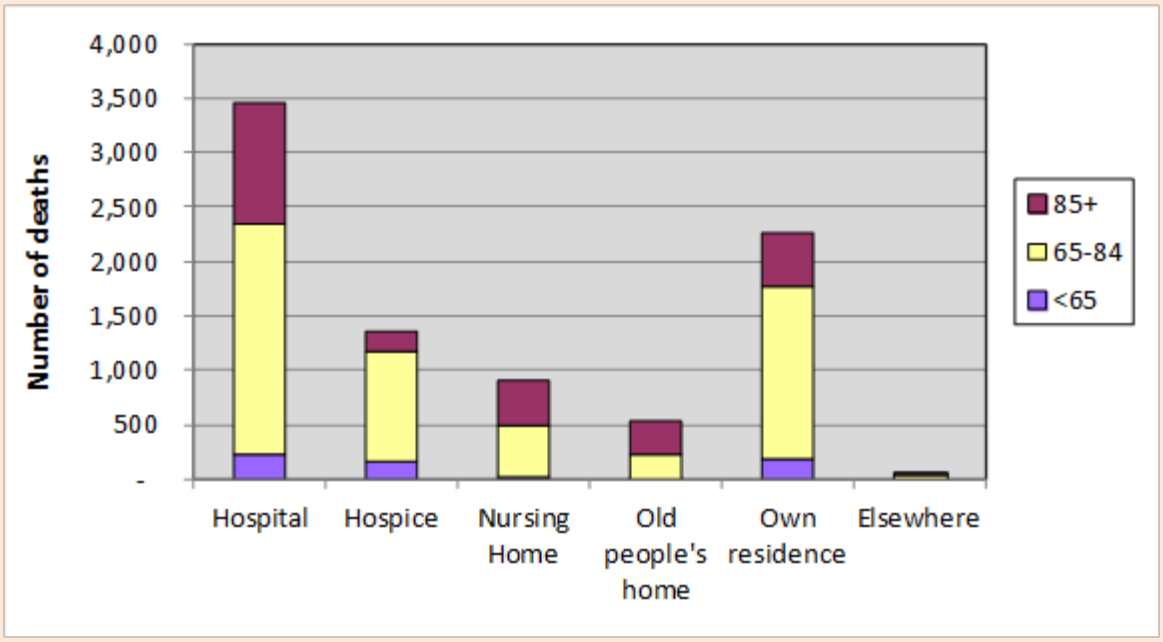
1.1.34 Mortality by ethnicity

Data up to 2008 suggests an age-standardised mortality rate in White men of 70.5 per 100,000, compared to 24.2 per 100,000 in the whole population (based on broad age bands). The mortality rate in Black men was found to be 30% higher than in White men ($p<0.01$) at a rate of 91.6 per 100,000. The mortality rate in men from India, Pakistan and Bangladesh was found to be only a quarter of that in White men, at 17.2 per 100,000 ($p<0.01$). This is consistent with a low mortality rate in India, Pakistan and Bangladesh as found by the GLOBOCAN project and may be due to the shorter life expectancy in these countries with many men dying of other causes (National Cancer Intelligence Network 2012).

1.1.35 Mortality by place of death

In 2010, the greatest number of deaths due to prostate cancer occurred in hospital, followed by the patient's own residence (3,611 and 2,351 deaths respectively) (see Figure 18). Deaths due to prostate cancer were most likely to occur in hospital in those aged <65, 65-84 and 85+ years (37%, 39% and 43% of all prostate cancer deaths respectively). The proportion of deaths due to prostate cancer which occurred in a hospice decreased with increasing age (28%, 18% and 8% in those aged <65, 65-84 and 85+ years). While the proportion occurring in a nursing home or old people's home increased with age (4%, 13% and 29% respectively).

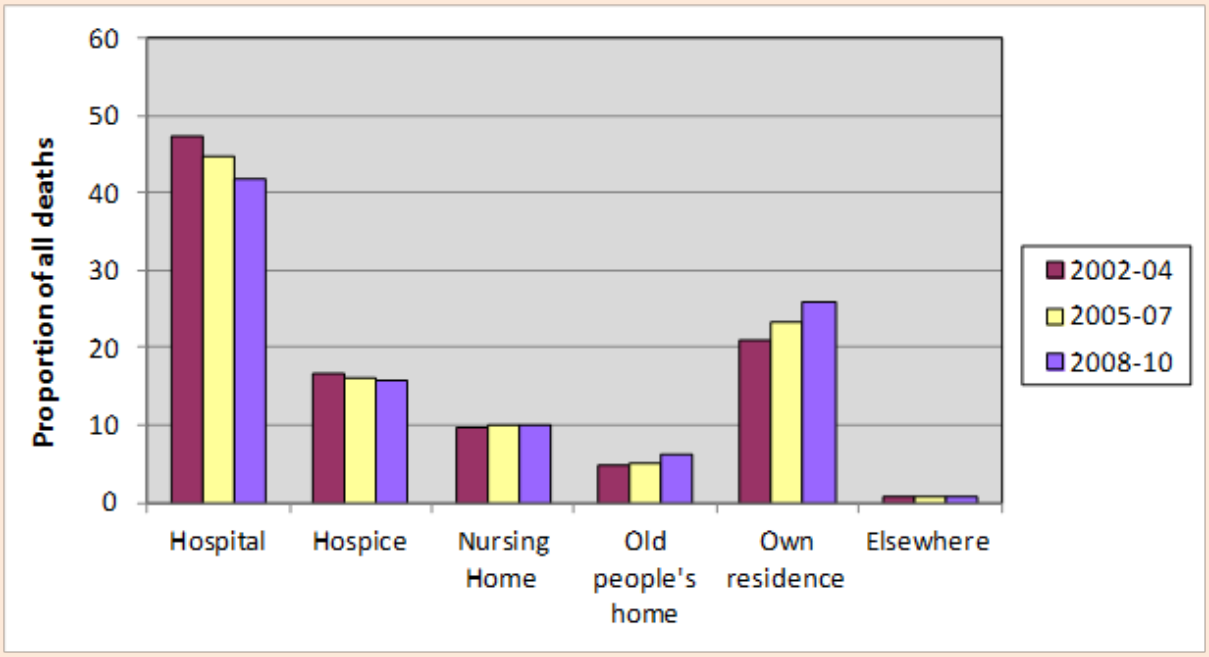
Figure 18: Number of deaths due to prostate cancer by place of death, 2010 (source: SWPHO)



Since 2002-2004 there has been a decline in the proportion of prostate cancer deaths which occur in hospitals (from 47% to 42%) and a slight decline in the proportion occurring in hospices (see Figure 19). This is a result of an increase in the proportion of prostate cancer deaths which occurred the patient's own residence (from 21% to 26%) and a slight increase in the proportion occurring in old people' homes. The proportion of prostate cancer deaths occurring in nursing homes has remained at 10%.

Update 2014

Figure 19: Proportion of all deaths due to prostate cancer by place of death, 2002-2010 (source: SWPHO)

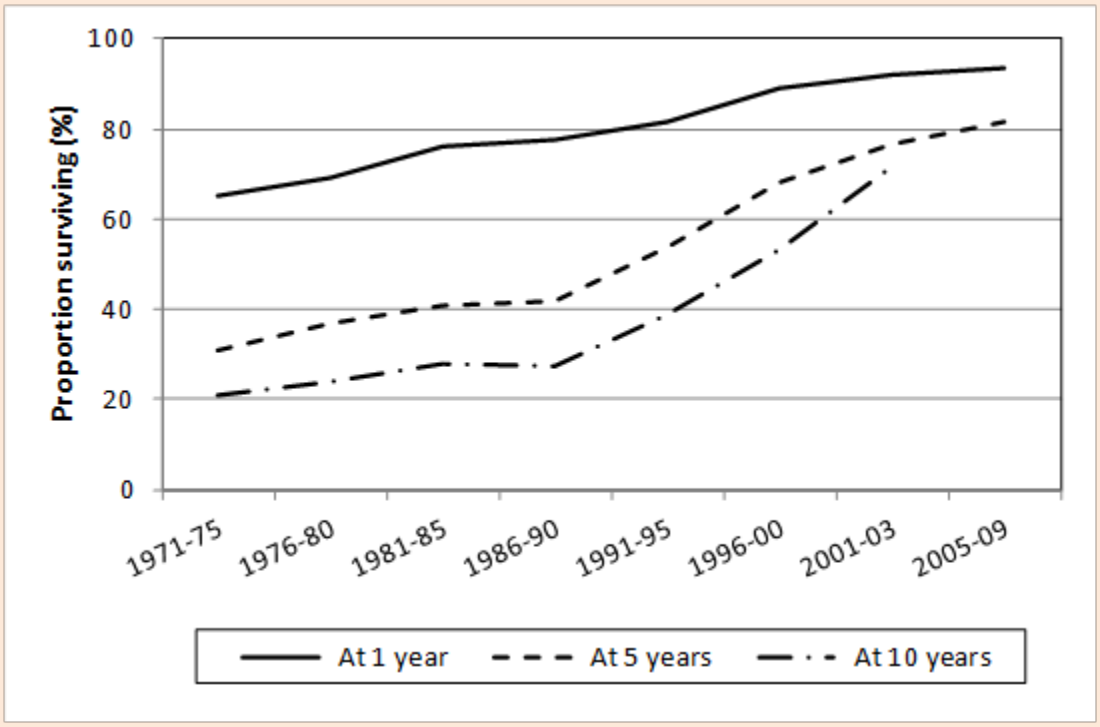


1.1.14 Survival

Prostate cancer prevalence is predicted to increase at the fastest rate of all cancers among males in the UK, even when assuming incidence rates from 2009 remain static. The number of prostate cancer survivors is estimated to reach 831,000 by the year 2040 with an average annual increase of 5.0% between 2010 and 2020 (assuming dynamic incidence rates) (Maddams *et al*. 2012).

The 1-, 5- and 10-year survival rates for adults in England aged between 15 and 99 years are estimated to be 94%, 81% and 69% respectively for patients diagnosed between 2005 and 2009[b]. The 5-year age standardised survival for prostate cancer patients diagnosed between 2005 and 2009 is the third highest in men of the 21 most common cancers. Only cancer of the testis, melanoma of the skin, and Hodgkin lymphoma have higher survival rates at 97%, 84% and 82% respectively (Office for National Statistics 2013). Figure 20 shows a steady improvement in survival rates since 1971 at 1, 5 and 10 years, with 5- and 10-year survival improving at a greater rate since 1990.

Figure 20: Age standardised survival rates for prostate cancer patients in England and Wales, 1971-2009 (source: Cancer Research UK)



From 1971-1995 survival is estimated for England and Wales; post-1995 survival is for England alone. Ten-year survival rates are not age standardised 1971-1985. All 5-year survival rates are not age-standardised

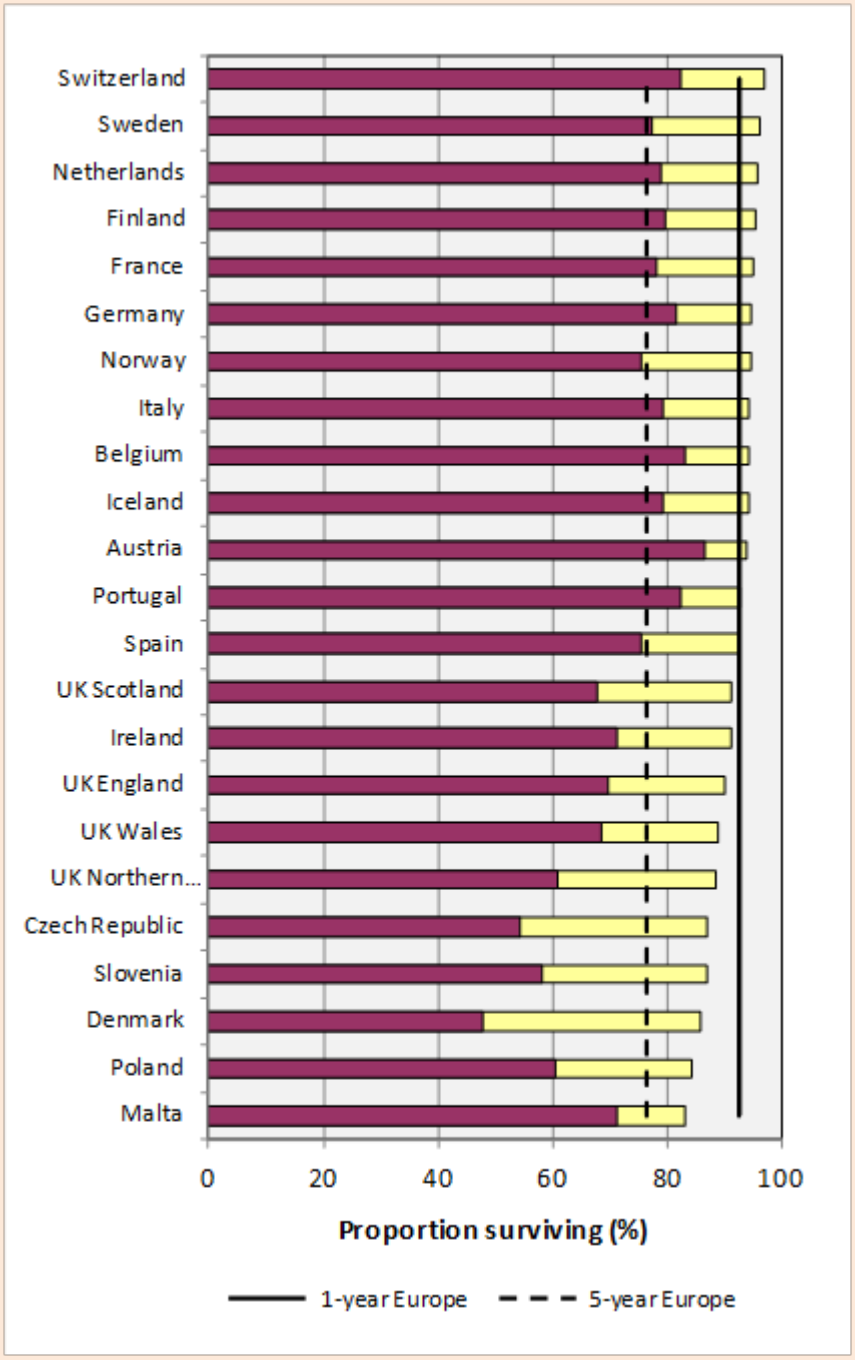
Between-country differences in survival in Europe have been shown to be some of the widest for any cancer (Sant *et al*. 2009). This may be due to wide differences in stage at diagnosis as some parts of Europe are diagnosing asymptomatic cancer. Figure 21 shows data from the Eurocare-4 project which aims to standardise cancer survival data across Europe to enable meaningful comparisons between countries. It is important to be aware that while countries such as the UK have population-based cancer registries approaching 100% coverage, others use regional registries with population coverage of less than 10% and data may not be representative of the country as a whole. There are also variations in data collection and diagnostic practices across Europe.

Update 2014

b 1- and 5-years survival rates are based on those diagnosed between 2005 and 2009 in England. The 10-year survival rate is based on those diagnosed in 2007 in England and Wales

Survival at 1 year was highest in Switzerland and lowest in Malta (97.1% and 83.0% respectively). Survival at 5 years was highest in Austria and lowest in Denmark (86.7% and 47.7% respectively). The overall survival rate for Europe at 1 and 5 years was 92.7% and 76.4% respectively. The greatest decrease in the estimated proportion of prostate cancer patients surviving between 1 and 5 years was in Denmark and the smallest decrease seen was in Austria (38.3% and 7.2% respectively). The overall survival rate for Europe decreased by 16.3%.

Figure 21: Age standardised relative survival of prostate cancer patients diagnosed 1995-1999 at 1 and 5 years by European country (source: Eurocare-4)



1.1.11 Survival by Cancer Network

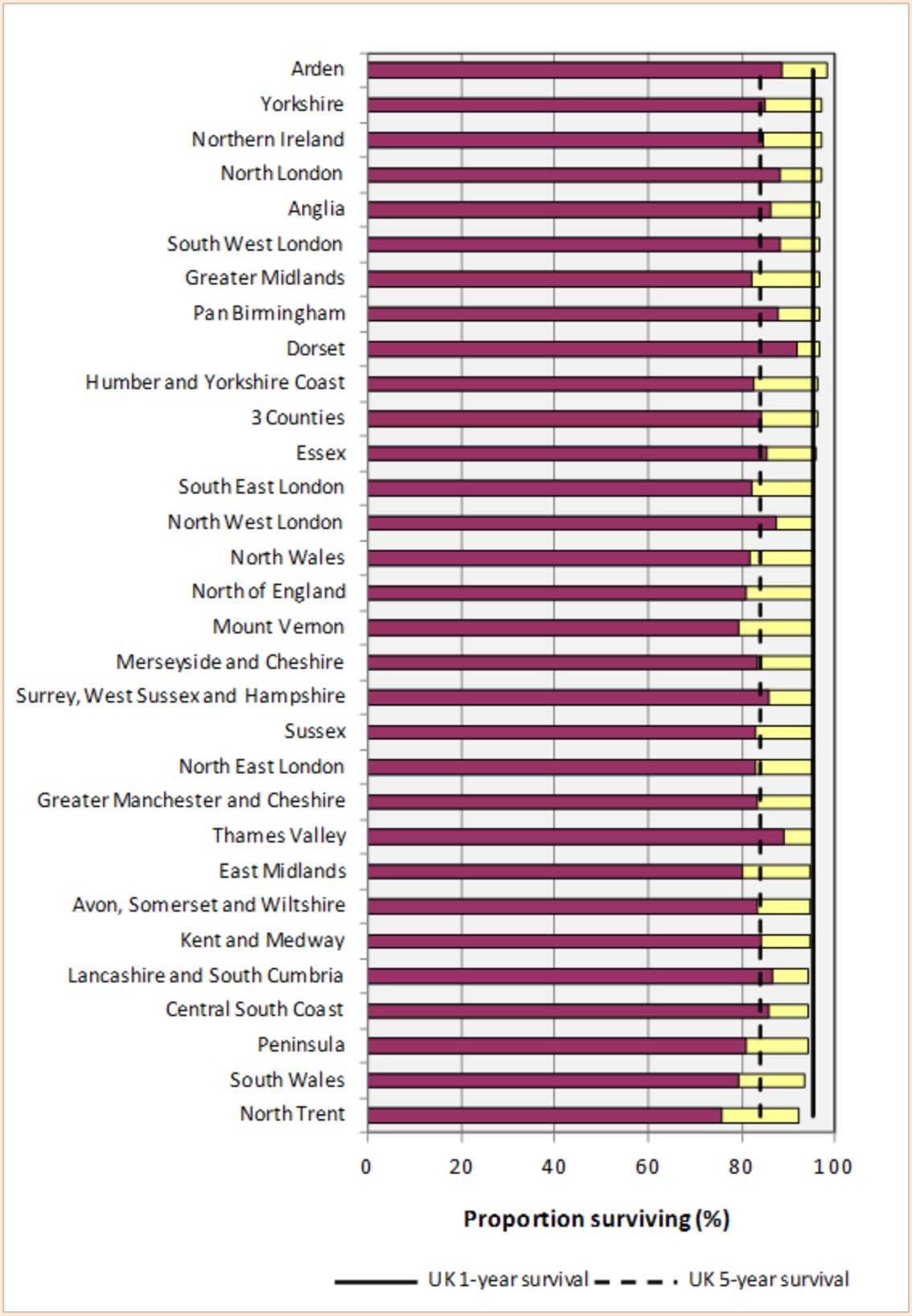
Figure 22 shows the variation in relative survival of prostate cancer patients across the Cancer Networks in the UK. Relative survival at 1 year was highest in Arden and lowest in

Update 2014

North Trent (98.3% and 92.4% respectively). Relative survival at 5 years was highest in Dorset and lowest in North Trent (91.8% and 75.5% respectively). These were significantly different from the overall relative survival rate for the UK at 1 and 5 years (95.4% and 83.8% respectively; $p<0.05$). The greatest decrease in the estimated proportion of prostate cancer patients surviving between 1 and 5 years was in North Trent and the smallest decrease seen was in Dorset (16.9% and 4.7% respectively). The overall relative survival rate for England decreased by 11.5%.

Update 2014

Figure 22: Prostate cancer relative survival of patients diagnosed 2001-2005 and 2005-2009 at 1 and 5 years respectively in the UK by Cancer Network (source: NCIN)



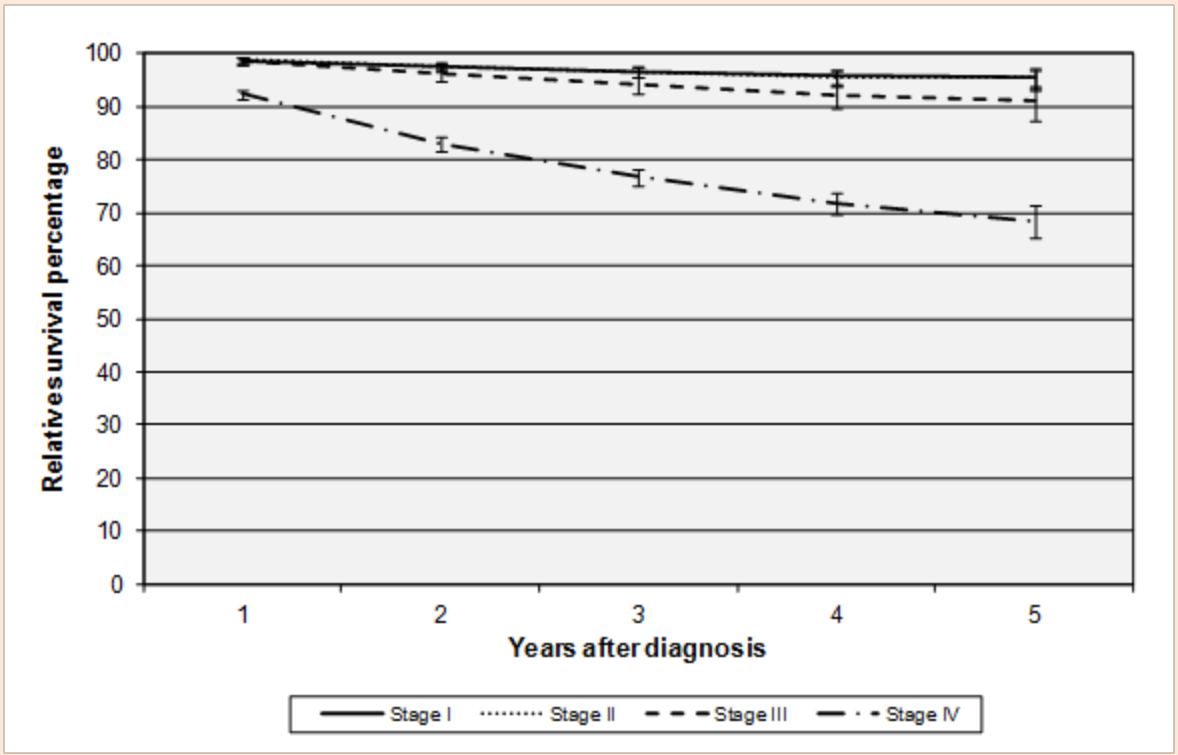
Rates are adjusted for age, sex and geographical region

Update 2014

1.1.412 Survival by stage at diagnosis

Based on a cohort of men diagnosed with prostate cancer in England 2003-2005, the 5-year relative survival was found to be 95%, 96%, 87% and 69% for those diagnosed with stage I, II, III and IV respectively (see Figure 23). The largest decrease in relative survival over the 5 years following diagnosis was seen in those with stage IV; decreasing from 92% at 1 year to 69% at 5 years.

Figure 23: Relative survival of prostate cancer patients diagnosed 2005-2009 in England by stage and years following diagnosis (source: NCIN)

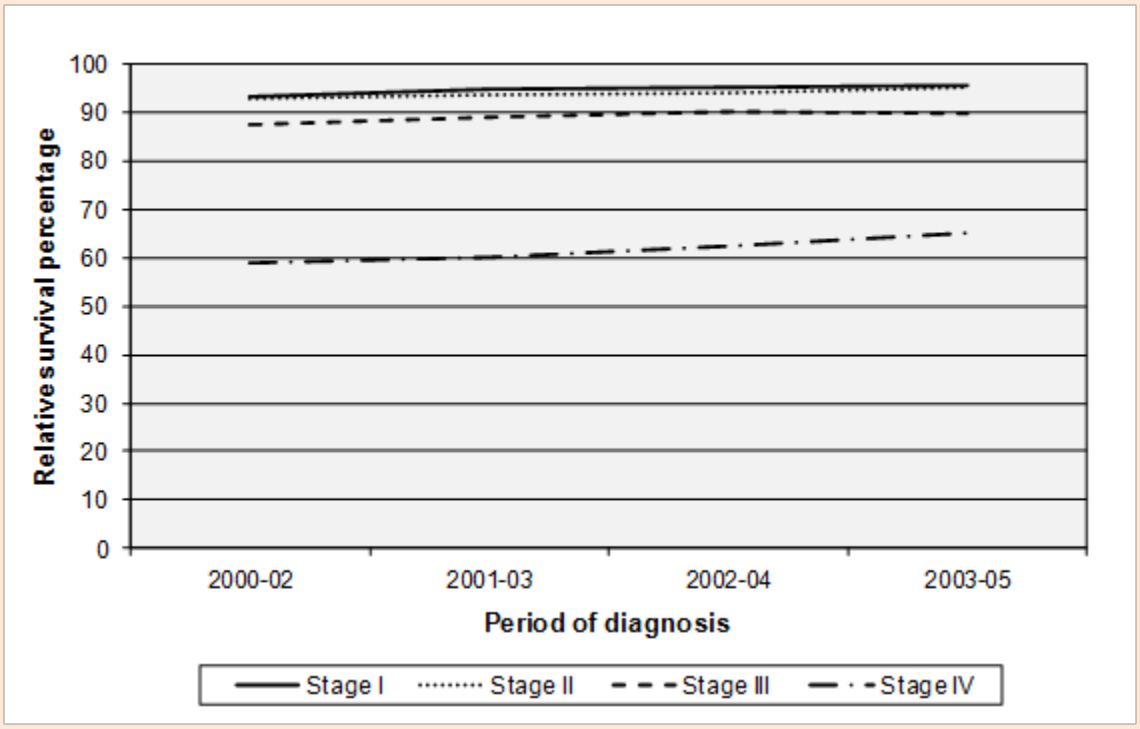


Mapping from TNM stage to numerical stage was conducted according to the TNM Classification of Malignant Tumours manual by the International Union Against Cancer (International Union Against Cancer 2009). Stages are defined using the full TNM classification of malignant tumours procedure advocated by the IUCC: stage I = T1-T2a N0; stage II = T2b-T2c N0; stage III = T3 N0; stage IV = T4 N0 or any T & N1 or any T, any N & M1

Figure 24 shows relative survival by stage of those diagnosed during different time periods. Over time there has been a significant increase in the proportion of patients diagnosed with stages II and IV who survive to 5 years ($p<0.02$). This is most notable in those diagnosed with stage IV disease with the proportion surviving to 5 years having increased by 10% between 2000-02 and 2003-05.

Update 2014

Figure 24: Relative 5-year survival of prostate cancer patients diagnosed 2000-2005 in England by stage and time period of diagnosis (source: NCIN)



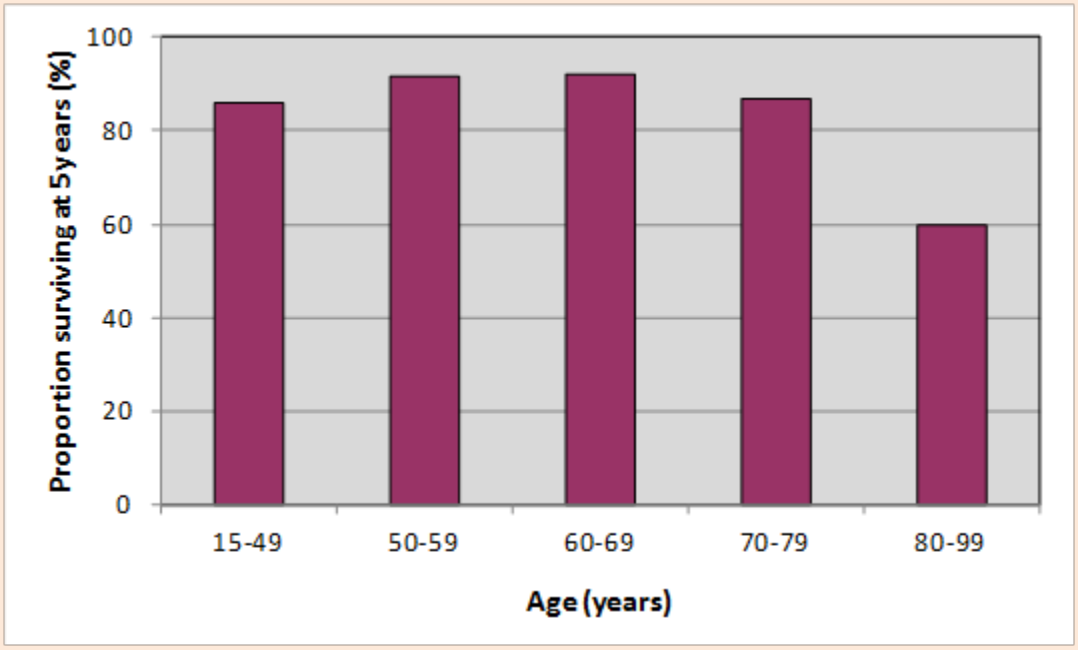
Mapping from TNM stage to numerical stage was conducted according to the TNM Classification of Malignant Tumours manual by the International Union Against Cancer (International Union Against Cancer 2009). Stages are defined using the full TNM classification of malignant tumours procedure advocated by the IUCC: stage I = T1-T2a N0; stage II = T2b-T2c N0; stage III = T3 N0; stage IV = T4 N0 or any T & N1 or any T, any N & M1

Update 2014

1.1.493 Prostate cancer survival by age

Studies have shown age at diagnosis to be a significant predictor of overall survival in men with prostate cancer (Bechis *et al*. 2011). This is likely to reflect the impact of other variables such as comorbidities, increased susceptibility to major illness, and decreased immune response. Figure 25 shows 5-year relative survival to be highest in those aged 50-69 years (91-92%), dropping to only 60% in those aged 80-99 years.

Figure 25: Relative survival of prostate cancer patients diagnosed 2005-2009 in England at 5 years (source: Cancer Research UK 2012)

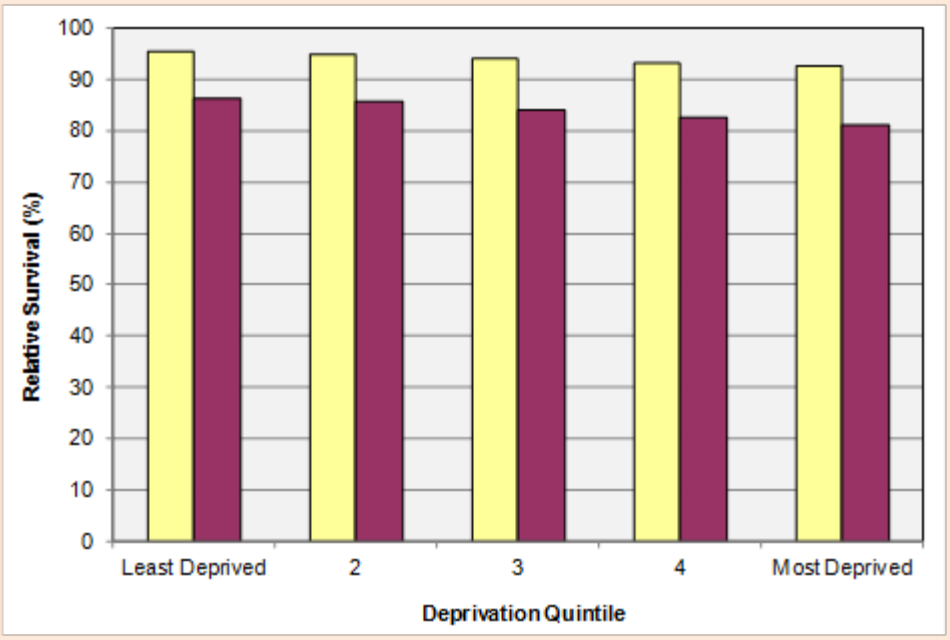


1.1.4.4 Survival by socioeconomic deprivation quintile

Survival estimates based on patients diagnosed between 2002 and 2006 show decreasing survival rates with increasing income deprivation at both 1 and 5 years (p=0.001) (see Figure 26). This difference equates to 86% of those in least deprived quintile surviving at 5 years compared to 81% in the most deprived quintile.

Update 2014

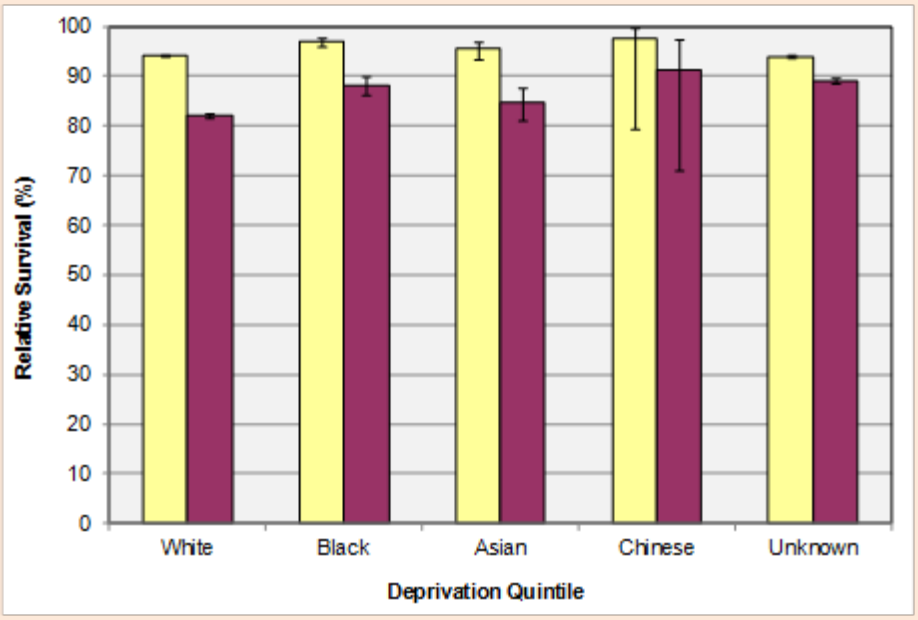
Figure 26: Relative survival of prostate cancer patients diagnosed 2002-2006 in England at 1 and 5 years by quintile of income deprivation (source: NCIN)



1.1.415 Survival by ethnicity

Survival estimates for different ethnic groups show no statistical difference due to the high proportion of patients whose ethnic group is not reported (see Figure 27). It is therefore difficult to determine any trends.

Figure 27: Relative survival of prostate cancer patients diagnosed 2002-2006 in England at 1 and 5 years by ethnic group (source: NCIN)



1.1.815 Quality of life of prostate cancer survivors

The patient-reported outcome measures (PROMs) study of cancer survivors 1-5 years following diagnosis reported that 38.5% of prostate cancer respondents had some degree of urinary leakage, 12.9% reported difficulty controlling their bowels, and 58.4% were unable to have an erection. A further 11.0% reported significant difficulty in having or maintaining an erection. The presence of urinary leakage was found to be significantly associated with lower quality of life scores (Glaser *et al*. 2013).

The PROMs study also found that patients with two or more long-term conditions or who were in the most deprived quintile (based on the IMD) were significantly associated with lower quality of life scores and increased social distress and difficulties (odds ratios of 4.28 and 2.57 respectively). However, prostate cancer survivors were shown to have significantly lower overall social distress scores and reported fewer problems in everyday living, money matters, and interaction with others compared with other types of cancer (Glaser *et al*. 2013).

1.1.916 Financial cost of prostate cancer

The impact of prostate cancer in an aging population is expected to increase, even if the incidence rate were to remain constant. The financial burden of treatment will therefore increase as the number of patients diagnosed increases. There will also be an increased need for resources such as treatment facilities and trained specialists. The mean direct costs per patient for initial treatment for prostate cancer have been estimated at around £2,505 in the UK. This compares to £2572 in Spain, £3,205 in Germany, £4,129 in Italy, and £4,622 in France (Fourcade *et al*. 2009). The total estimated costs for all patients in the first year from diagnosis were estimated to be £94.1 million in the UK (compared to £92.5, £196.9, £163.0 and £310.6 million in the other countries respectively). However, this does not include indirect costs, such as time and productivity lost through cancer-related illnesses, the impact

Update 2014

of the physical and mental suffering of both patients and relatives during diagnosis and follow-up, or end-of-life costs.

Prostate cancer patients have also been shown to have more emergency than elective admissions during their last year of life (National End of Life Care Intelligence Network 2012). In those dying from prostate cancer, the average final admission cost is nearly half (47%) of the average total last year of life cost (National End of Life Care Intelligence Network 2012). The estimated total cost of inpatient care per person during their last year of life is reported to be £6,931 for prostate cancer (see Table 6).

Table 6: Admissions, length of stay and cost in the last year of life, for men dying from prostate cancer in 2006–08 (source: National End of Life Care Intelligence Network 2012)

	Elective	Emergency	Total
Admissions in the last year	8,181	41,829	50,010
Bed days in the last year of life	69,482	530,288	599,770
Average length of stay per admission	8.5	12.7	12.0
Average admissions per person	1.4	2.1	2.4
Length of stay on final admission	13.3	15.7	15.5
Total Cost (£)	**15,553,710**	**126,574,654**	**142,128,364**
Cost per admission (£)	1,901	3,026	2,842
Cost per person (£)	2,691	6,448	6,931
Cost of final admission (£)	2,409	3,323	3,223

Update 2014

1.2 Diagnosis and investigations

The four procedures which are commonly used as diagnostic tests for prostate cancer are digital rectal examination (DRE), the PSA blood test, transrectal ultrasound (TRUS), and needle biopsy. DRE procedures are very common but information on this is not routinely collected. Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is about 0.2 mL or larger (European Association of Urology 2011). A suspect DRE is usually an indication for prostate biopsy which commonly involves needle biopsy in conjunction with TRUS. Radiological screening, including computerised tomography (CT) and magnetic resonance imaging (MRI) are also often used to aid diagnosis and staging.

1.2.1 Prostate-specific antigen (PSA) testing

Men in the UK can request a PSA test at their general practice, however, the level of PSA testing is not currently centrally monitored. Surveys of general practices and pathology labs carried out in recent years have suggested a testing rate of around 6% per year among 45-89 year-old men with no previous diagnosis of prostate cancer (Williams *et al*. 2011; Pashayan *et al*. 2006; Mokete *et al*. 2006; Melia *et al*. 2004). The consistency of survey results suggest that rates of PSA testing have varied little over the last decade.

Testing rates vary by age and by geographical location; testing rates of 1.4% have been found in those aged 45-49 years, rising to 11.3% in those aged 75-79 years (Williams *et al*.

2011). The rate of PSA testing has also been shown to independently decrease with increasing proportion of either black or Asian populations (Melia *et al*. 2004). In black populations the incidence of prostate cancer is higher than the average for England while in Asian populations it is lower.

Men attending general practices in more affluent areas have been shown to be more likely to undergo a PSA test, which suggests that uptake may not reflect clinical need (Williams *et al*. 2011). For example, Williams *et al*. 2011 found a strong inverse relationship between PSA testing rate and the relative social deprivation of the area surrounding that practice. However, the link itself between testing rate and social deprivation is unclear. Studies have found no correlation with educational status or monthly household income after controlling for age (Haidinger *et al*. 1999). It may be that higher testing rates reflect more screening requests by asymptomatic men. There is evidence to suggest that men from higher socioeconomic backgrounds are more likely to be aware of the PSA test and to have discussed prostate cancer screening with a healthcare professional (The Prostate Cancer Charity 2009). A survey by Melia *et al*. 2004 between 1999 and 2002 reported testing rates of 2.0% in asymptomatic men, 2.8% in symptomatic men, and 1.2% for re-testing. This suggests that a third of PSA tests conducted in general practice may be on asymptomatic men.

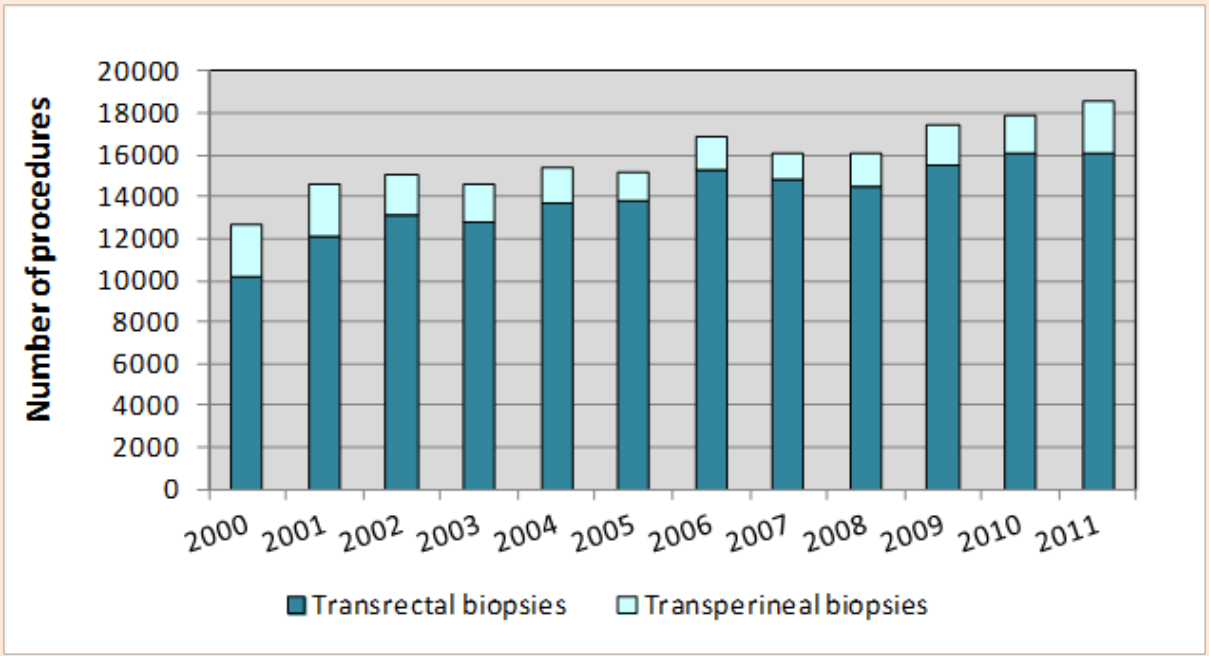
The Prostate Cancer Risk Management Programme (PCRMP) has performed two surveys of 210 laboratories that participate in the UK National External Quality Assessment Service (NEQAS) scheme (UK NEQAS). A subgroup of 79 laboratories responded to the survey in both 2000-01 and 2003-04 and reported an increase of 39% in the number of PSA tests conducted. The origin of samples for PSA testing varied significantly between laboratories. However, the mean proportion of test samples collected by General Practitioners in 2003-04 was 52%, with 31% of samples submitted by a Urologist and 16% by other Consultants (Prostate Cancer Risk Management Programme, accessed 2012; Prostate Cancer Risk Management Programme, accessed 2012). There was a small but statistically significant increase in the proportion of tests which were requested by GPs between the two surveys.

Update 2014

1.2.2 Initial biopsy

Diagnosis of prostate cancer in the UK is confirmed using a needle biopsy. Biopsy is recommended for men with a serum PSA above a diagnostic threshold currently set at 3 ng/ml for men in their 50s, 4 ng/ml for those in their 60s and 5 ng/ml for those in their 70s (NHS Cancer Screening Programmes 2012; Oesterling *et al*. 1993). The biopsy is an outpatient procedure which is most often conducted as a transrectal needle biopsy under TRUS guidance and antibiotic prophylaxis to gain 10-12 cores of prostate tissue for a histopathological diagnosis.The number of needle biopsies conducted in England has shown a relatively steady increase over the last 10 years and numbers follow the same trend seen in incidence (see Figure 28).

Figure 28: Number of transrectal and transperineal needle prostate biopsies performed as inpatient or day case procedures in England, in patients diagnosed with cancer, 2000-2011 (source: HES)



Identified using OPCS-4 codes M703 (transrectal) and M702 (transperineal). Where patients were reported to undergo both transrectal and transperineal biopsy in the same episode (104) this was classed as transperineal.

The majority of tumours are located in the peripheral zone of the prostate, however, some do occur elsewhere such as in the transitional or central zone. TRUS is poor at detecting anterior, apical and central lesions which limits its usefulness (Norberg *et al*. 1997). At present, approximately 25% of men undergoing biopsy with PSA levels above threshold will have cancer detected (Ramsey *et al*. 2012), though this varies depending on the biopsy protocol used. Detection rates are estimated at 14-22% for first biopsy, 10-15% for second biopsy, and 5-10% for third biopsy (Djavan *et al*. 2005; Mian *et al*. 2002; Lujan *et al*. 2004).

Current European Association of Urology (EAU) guidelines recommend an extended scheme as the initial biopsy strategy and reserving saturation protocols to repeat biopsy (European Association of Urology 2011). The role of saturation schemes involving more than 20 cores and including additional lateral peripheral and midline peripheral sampling remains controversial, as some studies demonstrated (Guichard *et al*. 2007; Scattoni *et al*. 2010) while others failed to demonstrate diagnostic advantages of saturation over extended schemes (Eichler *et al*. 2006; Jones *et al*. 2006; Pepe and Aragona 2007). For example, Cormeo *et al*. 2012 found no significant difference in the detection rate of 10-, 14- or 18-core schemes (39%, 42% and 42% respectively), however, there was a significant difference between these and a 6-core scheme (33% detection rate). There is no routinely-collected information on the number of cores collected at biopsy in the UK, however, standard agreed practice is to take 10-12 cores.

1.2.261 Transperineal biopsy

There was a significant reduction in the proportion of biopsies undertaken in England which were transperineal from 29% in 2000 to 8% in 2007 ($p<0.001$), since then there has been a significant increase to 13% of all prostate biopsies in cancer patients ($p=0.04$) (see Figure 28). Sampling in the anterior zone of the prostate is thought to be improved with transperineal template biopsies, though some studies report similar rates to rectal biopsies (Takenaka *et al*. 2008; Hara *et al*. 2008).

Update 2014

Most sampling and imaging techniques have been introduced at a local level based on facilities available, rather than a systematic approach and use of transperineal template biopsy is varied. A survey of current guidelines for the use of template biopsy held by the Cancer Networks in England and Wales was undertaken November 2012 to January 2013; the response rate was 60%. It was assumed that all transperineal biopsies are perfeormed using a template. Of the Cancer Networks who responded, eight (44%) stated that there was no written Network guidance or policy relating to template biopsy, six (33%) provided details of their template biopsy policy, six (33%) provided details of a template biopsy policy specific to a particular Hospital or Trust, two (11%) reported that they used the EAU guidelines in the absence of their own policy, two (11%) reported standard practice in their Network (in the absence of a policy), and one (6%) provided their Urology Clinical Guideline which made no reference to template biopsy.

Of the ten template biopsy policies received, one (10%) did not recommend its use while another Network without a policy stated that this was because there was no funding for template biopsy. In eight (80%) of the policies, template biopsy was recommended for patients who had had a previous negative or equivocal transrectal TRUS biopsy but in whom prostate cancer was still suspected (in three of the policies this was specified as a rising PSA and in two suspicious areas on the MRI). The two Networks which reported standard practice also followed this policy. However, one of the policies required at least two negative TRUS biopsies before template biopsy was used. Further requirements for a template biopsy included: patients who were suitable for radical therapy only (20%); and a risk level > 12 based on PSA, DRE, appearance on TRUS, and TRUS calculated volume (10%).

Three (30%) of the policies and the two Networks reporting standard practice also allowed for the use of template biopsy in patients on or beginning an active surveillance (AS) regime. In one policy patients on active surveillance were required to be at low-risk, while in another a previous Gleason score of 6, volume < 5%, static PSA, and suitability for radical therapy was required. The third policy was to offer template biopsy to those considering AS with minimal amounts of prostate cancer on prior TRUS biopsy and to those on AS with suspicion of progression. Standard practice in one Network was to use template biopsy in men with localised disease who wished to undertake AS but were regarded as having high risk of under-staging by the transrectal biopsy. Standard practice in another was to perform template biopsy on all men being considered for AS following a diagnosis of low risk disease or low volume intermediate disease on prior TRUS biopsy.

One of the policies also allowed for template biopsy on men with a suspicion of prostate cancer who were unsuitable or unwilling to undergo transrectal TRUS biopsy, for example, those with inflammatory bowel disease or perianal sepsis. Standard practice in another Network was to undertake template biopsy in men with a prostate > 70 cc, with significant lower urinary tract symptoms (LUTS), who had received recent antibiotic therapy, had a lack of tolerance for transrectal biopsy, or who had any other complicating factor.

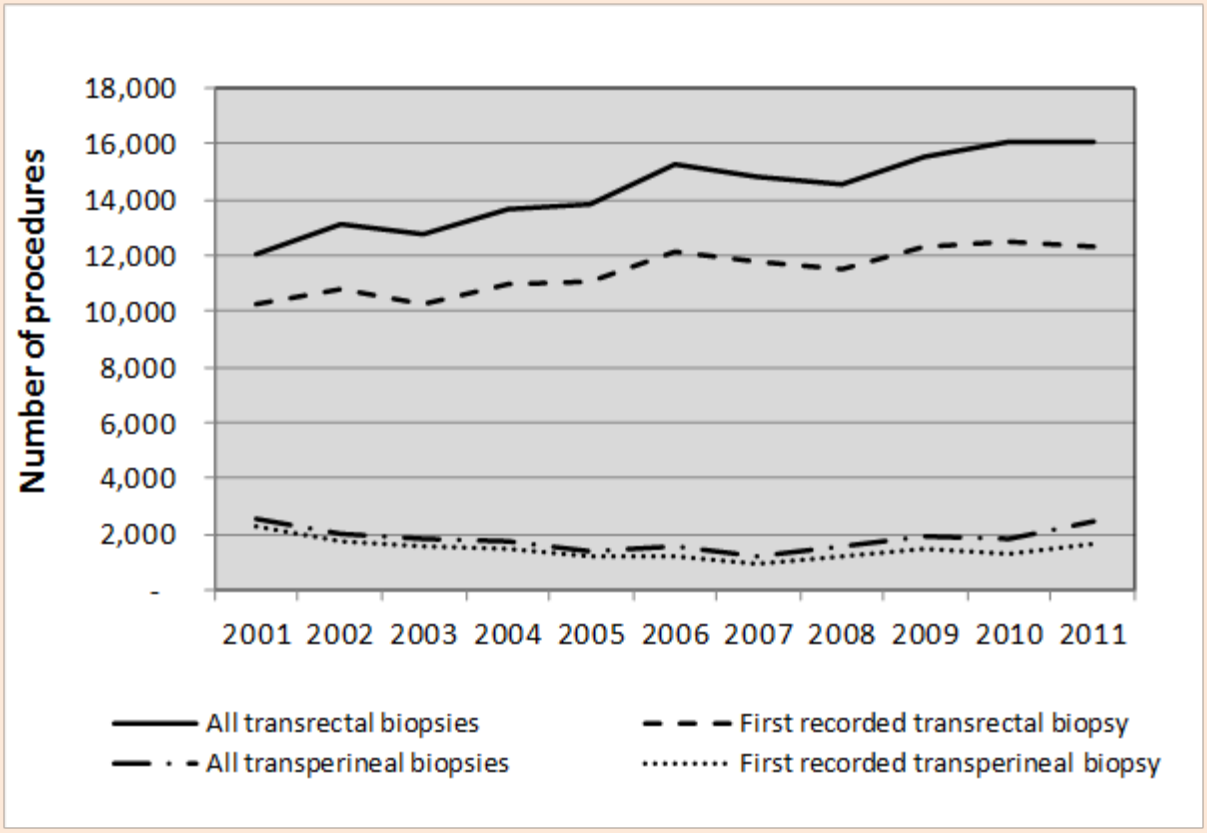
Update 2014

1.2.202 Repeat biopsy

Of those patients with a cancer diagnosis undergoing prostate biopsy as inpatients or day cases, the proportion which are the first recorded biopsy for that patient has decreased steadily from 93% in 1998 to 75% in 2011. This decrease can be seen for both transrectal and transperineal biopsies despite an overall increase in the number being undertaken (see Figure 29). However, this may reflect changes in recording practices rather than a large increase in the proportion undergoing repeat biopsies.

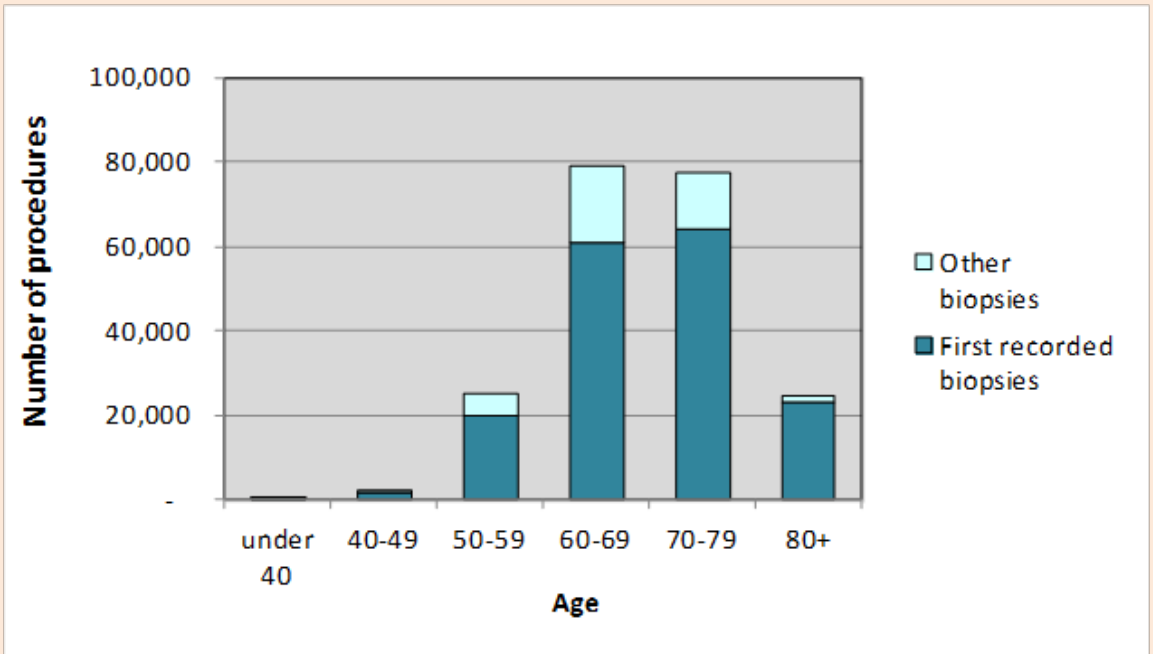
Where age is reported, the proportion of prostate biopsies which are the first recorded for that patient is highest in those aged under 40 or over 80 years (91% and 92% respectively) and lowest in those aged 60-69 years (77%) (see Figure 30). This trend can be seen for both transrectal and transperineal biopsies.

Figure 29: Number of transrectal and transperineal needle prostate biopsies performed as inpatient or day case procedures in England, in patients diagnosed with cancer, 2001-2011 (source: NCIN)



Identified using OPCS-4 codes M703 (transrectal) and M702 (transperineal). Where patients were reported to undergo both rectal and transperineal biopsy in the same episode (104) this was classed as transperineal

Figure 30: Number of transrectal and transperineal needle prostate biopsies performed as inpatient or day case procedures in England by age group, in patients diagnosed with cancer, 1998-2011 (source: NCIN)



Identified using OPCS-4 codes M703 (transrectal) and M702 (transperineal). Where date of birth was not available these patients were not included in the analysis (<0.1%).

Update 2014

1.2.3 Radiological screening

1.2.3.1 Magnetic resonance imaging (MRI)

Due to the high false negative rates associated with TRUS guided biopsy, if there is an interval rise in PSA following a negative biopsy, further investigation may be undertaken using MRI. The accuracy of staging of the disease may also be improved by MRI which can reduce unnecessary treatment-related morbidity when there is no possibility of cure (Sanchez-Chapado *et al*. 1997; Bates *et al*. 1997). Multi-parametric MRI may add additional information and can help to gauge suitability for active surveillance or feasibility of nerve-sparing surgery in low risk patients. In intermediate risk patients it can aid in identifying stage T3 disease, while in high risk patients an MRI of the spine may detect the degree of metastases.

A survey of current practice was conducted during January and February 2013. Details of the survey were sent to Cancer Networks and a contact at the Royal College of Radiology for escalation to all Consultant Radiologist members of the urological cancer multi-disciplinary teams (MDTs). Fifty-three Consultants from 47 different organisations responded, however, only 36 (68%) completed the full survey. The majority (94%) of respondents were employed by NHS Trusts or hospitals. Most (81%) worked in the NHS alone, while the remaineder were employed by both the NHS and private sector.

Thirty-six respondents (73% of those answering this question) reported using MRI for the detection of prostate cancer. Eighteen (50% of those using MRI for detection) used MRI prior to first biopsy, 14 (39%) prior to second biopsy, and 21 (58%) prior to a subsequent biopsy (10 used MRI at multiple points).

Forty-seven (89%) respondents reported using MRI at staging post-biopsy. Of these, 34 (72%) reported using PSA, in combination with other criteria, as the basis for their decision to undertake MRI, 21 (45%) reported using DRE findings with other criteria, 34 (72%) used the Gleason score (alone or in combination with other criteria), 15 (32%) used the number of positive cores, and 14 (30%) used the proportion of cores involved. Thirty-five (74%) used a combination of these methods, while 11 (23%) did not report using any of these five methods.

Of those that reported using PSA to help determine whether to use MRI for staging post-biopsy, 24 (71%) provided further information on their PSA threshold. Of these, 14 (58%) used a threshold of ≥ 10 ng/ml, four (17%) used a threshold of ≥ 15 ng/ml, and three (13%) ≥ 20 ng/ml. In three (13%) cases, no threshold was given as either all patients were considered for radical treatment or AS were given an MRI or the decision was based on multiple factors and likely treatment options.

Of those that reported using Gleason score to help determine whether to use MRI for staging post-biopsy, 23 (68%) provided further information on their threshold. Of these, 16 (70%) used a threshold of ≥ 7, though in two (9%) cases this was lowered to 6 if multiple cores involved and patient was aged < 65 years or if apices were involved. In two (9%) cases, no threshold was given as the decision was based on multiple factors and likely treatment options.

Of those that reported using the number of positive cores to help determine whether to use MRI for staging post-biopsy, seven (47%) provided further information on the threshold used. This ranged from > 3 to > 10-12 and is likely to be dependent on the number of cores taken at biopsy in practice. One respondent also reported a threshold of > 2 mm of a single core. Of those that reported using the proportion of cores involved to help determine whether to use MRI for staging post-biopsy, three (21%) provided further information on the threshold used. In two (67%) this was ≥ 50%, the other did not use a specific threshold but relied on multiple factors and likely treatment options.

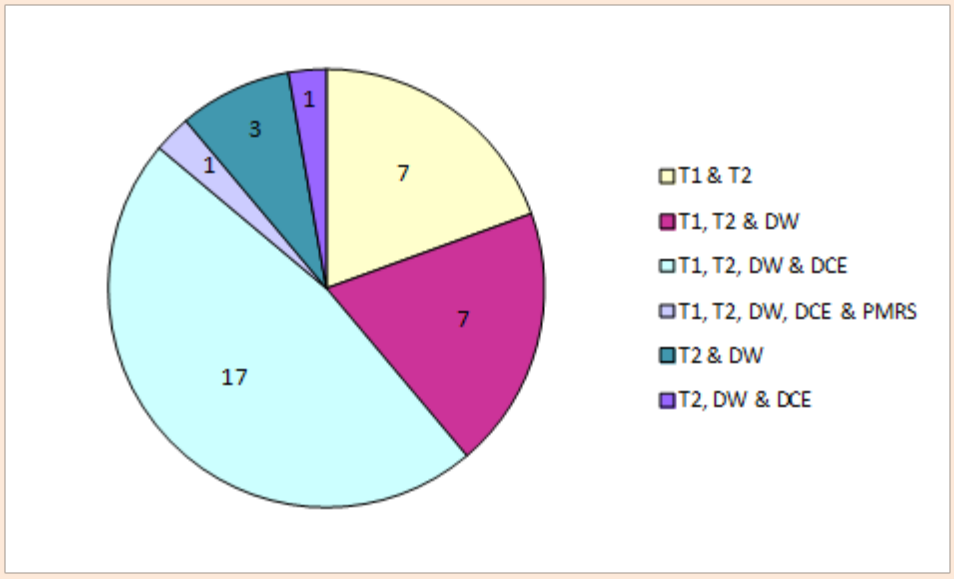
Update 2014

Thirty-two (76% of those answering this question) respondents reported using MRI at follow-up. Of these, 26 (81%) reported using MRI during active surveillance (AS), 24 (75%) following deep x-ray therapy (DXT), and 23 (72%) following prostatectomy. Twenty-two (85%) of those using MRI during AS provided further information on when MRI was used; 11 (34% of those using MRI at follow-up)) respondents reported undertaking MRI during AS following a rise in PSA, two (9%) undertook MRI annually, three (13%) if there was a possible change of management, three (13%) reported it to be variable, and three (13%) prior to next biopsy.

Twenty-one (88%) of those using MRI following DXT provided further information on when MRI was used; 17 (53%) respondents reported undertaking MRI following a rise in PSA, two (6%) following a risk in PSA or clinical symptoms, and one 3% following clinical symptoms. Twenty-one (91%) of those using MRI following prostatectomy provided further information on when MRI was used; 14 (44%) respondents reported undertaking MRI following a rise in PSA, five (16%) following a risk in PSA or clinical symptoms, and one (3%) following clinical symptoms.

Thirteen (25%) respondents reported that the use of MRI had reduced the number of biopsies undertaken while four (8%) reported that it had increased the number of biopsies. Seven (13%) reported that it had reduced the number of cores taken while three (6%) reported that MRI had increased the number of cores taken.

Figure 31: Proportion of survey respondents by MRI sequence used, 2013 (source: NCC-C)



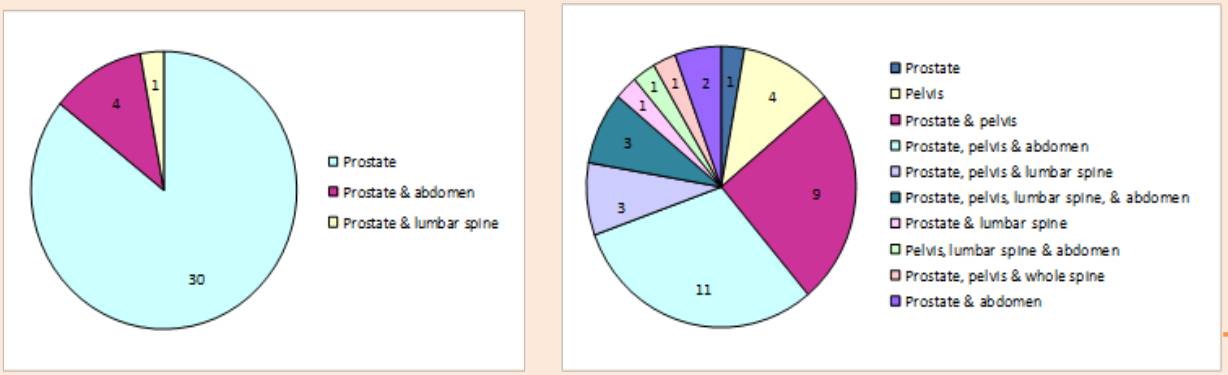
The survey found that of those who responded to the question (68%), all (100%) used T2, as well as either a T1 or a diffusion weighted sequence or both (see Figure 31). Seven respondents (19%) used T1 and T2, seven (19%) used T1, T2 and diffusion weighted, and 17 (47%) reported using T1, T2, diffusion weighted, and dynamic contrast-enhanced sequences. One (3%) reported using all four and proton magnetic resonance spectroscopy. Three (8%) reported using T2 and diffusion weighted sequences (without T1), while one (3%) used T2, diffusion weighted, and dynamic. Of those that responded to the question regarding the magnetic field strength used (68%), 34 (94%) reported using a field strength of 1.5-T. This included eight (22%) who reported using both 1.5-T and 3.0-T. Two (6%) respondents reported using <1.5-T field strength.

Eighteen (34%) respondents reported using a 16-channel phased array coil to improve staging performance. Twelve (23%) reported using an 8-channel phased array coil and one (2%) reported using an endorectal coil (it was unclear how many respondents chose not to

Update 2014

answer this question). Of those that responded to the question on where the MRI was directed for detection (62%), all (100%) reported directing it at the prostate. Four (12%) also reported directing it at the abdomen and one (3%) at the lumbar spine (see Figure 32). Of those that responded to the question on where the MRI was directed for staging (68%), the majority (75%) reported directing it at both the prostate and the pelvis. This includes 14 (39%) who also directed the MRI at the abdomen and six (17%) who also directed it at the lumbar spine. One (3%) respondent reported directing the MRI at the prostate alone and four (11%) at the pelvis alone. Two (6%) reported directing the MRI at the prostate and the abdomen and one (3%) at the prostate and the lumbar spine. One (3%) respondent reported directing the MRI at the pelvis, lumbar spine and abdomen (but not the prostate), and one (3%) reported directing the MRI at the whole spine together with the prostate and pelvis.

Figure 32: Proportion of survey respondents by direction of MRI during detection and staging (source: NCC-C)



It is important to note that two (4%) respondents commented that the answer options were too restrictive in the survey. It is also important to note that while some respondents reported using more than one MRI sequence or directing the MRI at more than one area, some choices are likely to be limited to intermediate or high risk populations.

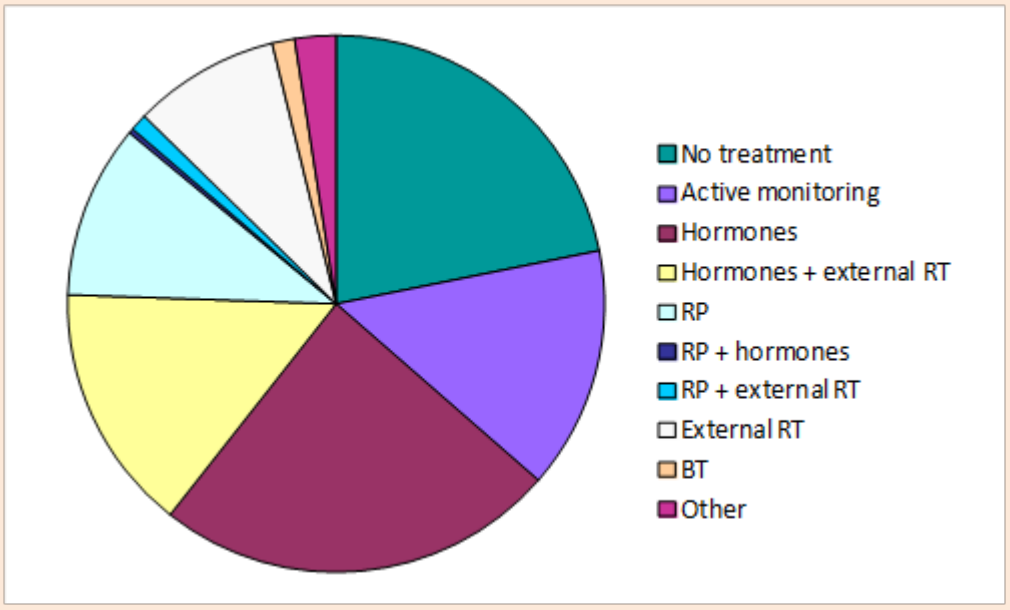
Update 2014

1.3 Current treatment options

Current evidence suggests that any benefit to an individual undergoing radical treatment for prostate cancer can take at least 10 years to accrue. Therefore these options may be best used for men whose comorbidity and age suggests a life expectancy of > 10 years (Ramsey *et al*. 2012). There is also evidence that more aggressive cancers, categorised by a Gleason score of ≥ 8 out of 10 and a PSA of > 20 ng/ml, are likely to already have developed metastases and therefore such patients are considerably less likely to benefit from radical treatment alone (Ramsay *et al*. 2012).

Current treatment consists of four main options: active surveillance, surgery, radiotherapy or androgen deprivation therapy (ADT) (also known as hormone therapy). Prostatectomy (surgical removal of the prostate), radiotherapy (RT), and ADT accounted for 61% of all patients diagnosed with prostate cancer in 2009 (see Figure 33). ADT was given to 39% of patients, though 15% of patients received hormone therapy in combination with external RT. Radiotherapy was given to 26% of men, most commonly in combination with ADT, with 9% of men receiving external RT alone and 1% receiving brachytherapy alone. Prostatectomy was used to treat 12% of men diagnosed in 2009, with only 1% of men undergoing prostatectomy and ADT or radiotherapy. The 'no treatment' group made up a large proportion (22%) of patients and included patients treated at private hospitals or where treatment was not recorded. Therefore these results should be treated with caution.

Figure 33: Proportion of men diagnosed with prostate cancer in 2009 in England by treatment type (source: NCIN)

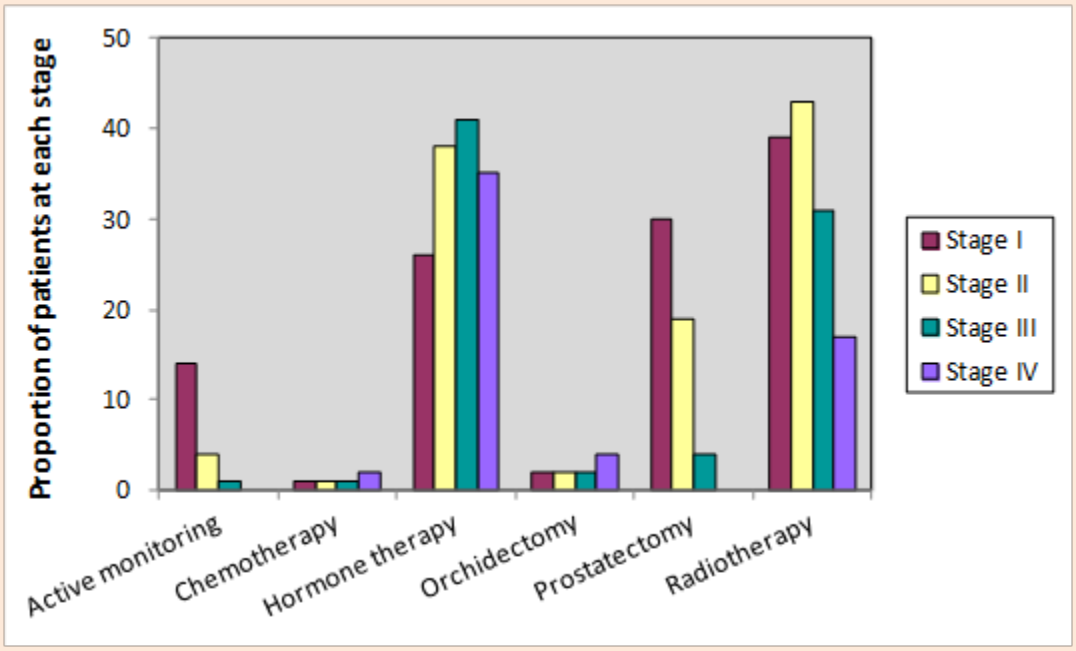


Active monitoring includes both active surveillance and watchful waiting. The no treatment group includes those treated at private hospitals and patients where treatment was not recorded.

Update 2014

Data from BAUS on men diagnosed in England in 2005 demonstrate the variation in treatment by stage at diagnosis (see Figure 34) (BAUS 2012). Patients diagnosed with stage I disease were most likely to undergo radiotherapy (39%), followed by prostatectomy (30%), hormone therapy (26%), and active monitoring (14%). Similar proportions of patients with stage II disease underwent radiotherapy and hormone therapy (43% and 38% respectively), with 19% undergoing prostatectomy and 4% active monitoring. For those with stage III disease, hormone therapy was the most common initial treatment (41%) followed by radiotherapy (31%), with ≤ 4% of patients receiving the other treatments. A similar trend was seen in patients with stage IV disease; with 35% receiving hormone therapy and 17% undergoing radiotherapy. More patients with stage IV disease underwent chemotherapy or orchidectomy than in any other stage.

Figure 34: Proportion of men diagnosed with prostate cancer at each stage in England in 2005, by treatment type (source: BAUS)



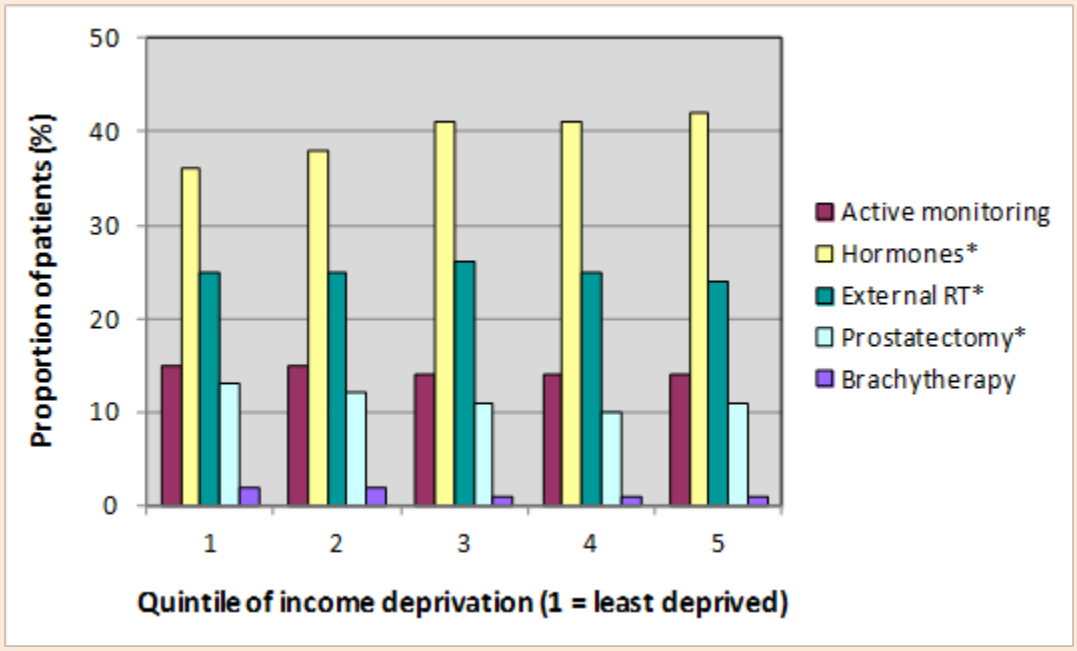
Active monitoring includes both active surveillance and watchful waiting. Patients may have surgical or non-surgical treatment, both or no treatment, therefore figures may not add to 100%.

Hormone therapy has been found to have significantly lower uptake in those of Asian ethnicity than in White men diagnosed for prostate cancer in England in 2009 (National Cancer Intelligence Network 2012). While the proportion of men undergoing prostatectomy was found to be significantly higher in Black or Asian ethnicity than in White men. The proportion of Black men receiving external radiotherapy was also significantly higher than the proportion of White men. However, reporting of ethnicity was poor and only 63% of men had a valid ethnicity assigned. Therefore results should be treated with caution.

There are no clear trends in treatment variation by quintile of income deprivation in patients diagnosed with prostate cancer in England (see Figure 35). The data suggest an increase of the use of hormone therapy with increasing deprivation. This may reflect earlier presentation of the disease in the least deprived patients as hormone therapy is generally reserved for advanced or relapsed cases. The proportion of patients undergoing prostatectomy or brachytherapy is slightly higher in the two least deprived quintiles which may again reflect more localised disease in these groups (National Cancer Intelligence Network 2012).

Update 2014

Figure 35: Proportion of men diagnosed with prostate cancer in 2009 in England by treatment type and quintile of income deprivation (source: NCIN)

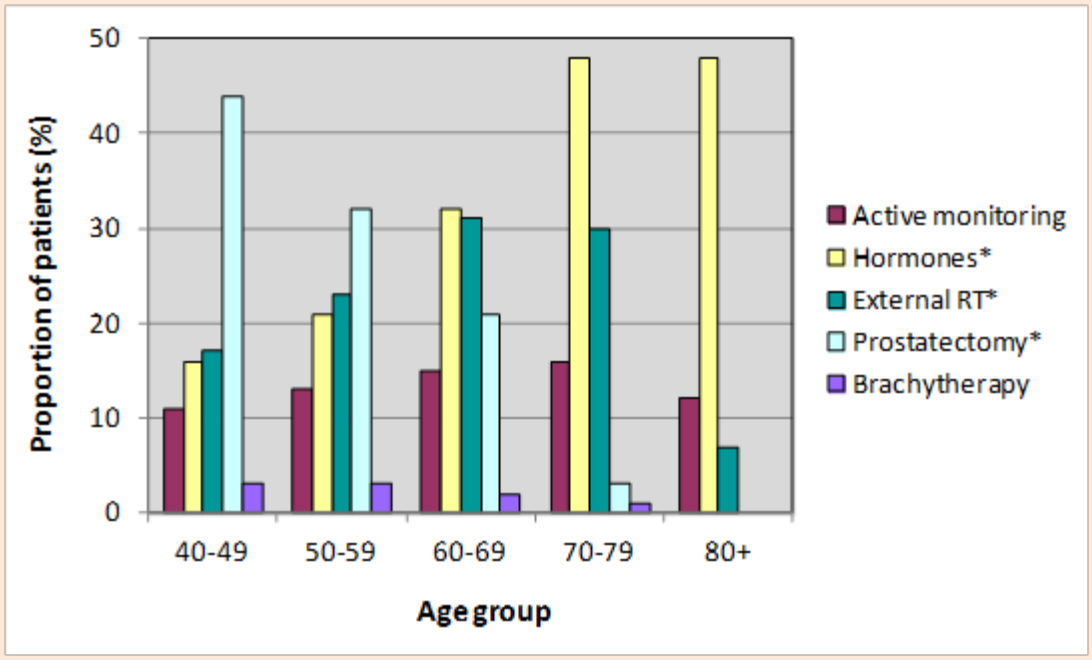


*Alone or in combination with another treatment type

Figures for 2009 suggest that the likelihood of receiving ADT, alone or in combination, increases with increasing age and is highest in those aged 70 years and over (see Figure 36). This is likely to reflect more advanced disease at presentation in older age groups and their reduced life expectancy. In contrast, the proportion of men undergoing prostatectomy, alone or in combination, decreases with age. This is likely to reflect more localised disease and greater life expectancy and benefit in the younger age groups. Use of brachytherapy also shows a slow decline with age which is consistent with the recommendation not to use this treatment in those with high risk localised disease.

Update 2014

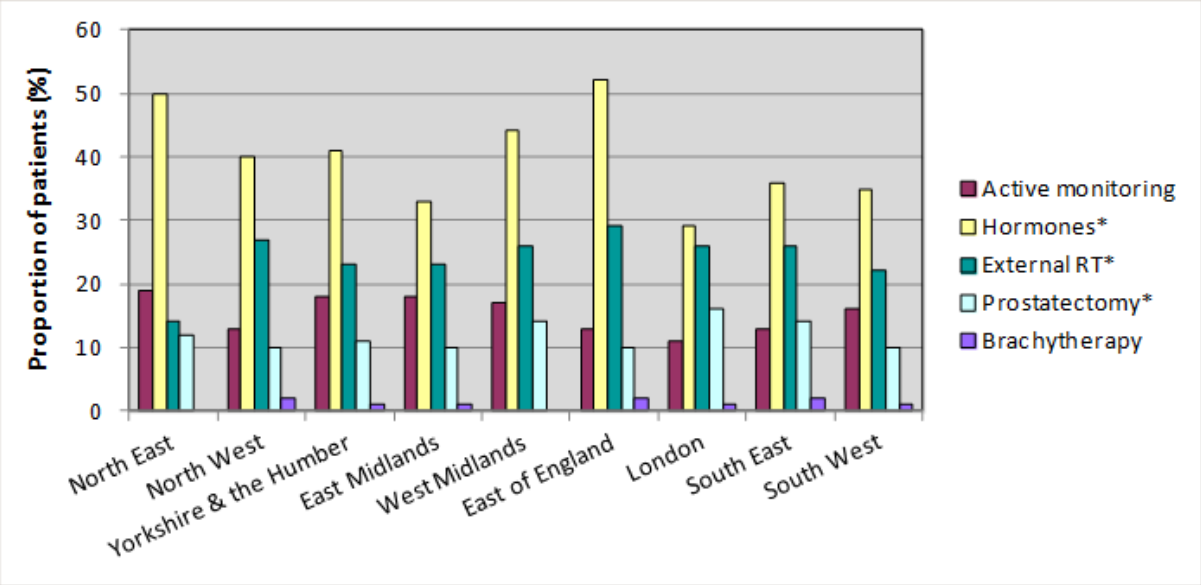
Figure 36: Proportion of men diagnosed with prostate cancer in 2009 in England by treatment type and age group (source: NCIN)



*Alone or in combination with another treatment type.

No correlation between treatment type and region of residence was found which suggests that personal and disease-related factors are of greater influence in treatment decisions (see Figure 37) (National Cancer Intelligence Network 2012).

Figure 37: Proportion of men diagnosed with prostate cancer in 2009 in England by treatment type and geographical region (source: NCIN)



*Alone or in combination with another treatment type.

1.3.1 Active surveillance

Active surveillance (AS) and watchful waiting are observational follow-up strategies which avoid immediate therapy in patients with prostate cancer. AS is curative in intent and suitable in men where the disease is believed to be indolent and does not require therapy. It involves the close monitoring of patients to avoid unnecessary treatment, which can be associated with significant short- and long-term complications, until disease progression occurs (or the patient requests treatment). In contrast, watchful waiting is palliative in intent and suitable for men in whom treatment is inappropriate due to comorbidity. Men with serious comorbidities which affect life expectancy, such as severe chronic pulmonary obstructive disease, end stage renal disease, or life limiting cancer, are unlikely to benefit from active treatment but may, at some stage, need intervention for disease control.

The previous NICE guidance on prostate cancer diagnosis and treatment (2008) recommended that men with low-risk localised disease who are considered suitable for radical treatment should first be offered active surveillance and that active surveillance should also be discussed as an option with men who have intermediate-risk localised disease (National Institute for Health and Clinical Excellence 2008). There are various ways of following up men with low risk prostate cancer. These include regular examination such as a DRE or the measurement of the PSA to look at PSA velocity, PSA doubling times or PSA density. Repeat biopsy may also be used. The previous clinical guideline GD58, recommended use of the follow-up protocol from the PROSTART study (examination and PSA testing at 3-monthly intervals for 2 years, and 6-monthly thereafter, with repeat TRUS-guided biopsies at 1, 4, 7 and 10 years), although no evidence was given to support this approach.

1.3.11 Eligibility for active surveillance

A survey of AS protocols currently in use by the 30 Cancer Networks in England, Wales and Northern Ireland was undertaken by NCC-C in 2012. A total of 24 protocols from 19 networks

Update 2014

were received; a response rate of 63%. Of the protocols received which specified eligibility criteria for engaging in AS, all (19 in total) used clinical T-stage as a criterion but varied widely in their definition. One (5%) protocol only included patients with stage T1a; three (16%) required patients to have stage T1c disease; four (21%) only included patients with either T1c or T2 disease; three (16%) required patients to have stage T2a or lower; another three (16%) protocols required patients to have stage T2b or lower; and three (16%) only included patients with stage T2c or lower. Two protocols (11%) required patients to have any stage T1 or T2.

Seventeen (89%) of the protocols also used Gleason score as a criterion. In one (5%) protocol patients were required to have a Gleason score < 6; in three (16%) patients had a score < 7; in five (26%) protocols any patients with a Gleason score < 8 were included. Five (26%) protocols required patients to have a Gleason score of 6, though they varied in their T-stage criteria, and two (11%) required patients to have a score of 6 or 7.

Sixteen (84%) of the protocols also set PSA level criteria; half (42%) of these only included patients with PSA < 10 ng/ml; three (16%) included patients with PSA < 20 ng/ml; two (11%) included patients with PSA < 0.15 ng/ml (both of which required patients to have stage T1c and Gleason 6); and one (5%) protocol each included patients with PSA < 11, < 15 and < 16 ng/ml.

Twelve (63%) of the protocols set further eligibility criteria; in six (32%) these were based on predicted survival and in six (32%) they were based on the number of cores positive or involved. Two (11%) protocols included certain exceptions to their eligibility criteria such as older frail patients, those with serious medical conditions, those that were asymptomatic, or who had a preference for AS.

Update 2014

1.3.1.2 Undertaking active surveillance

Twenty-three protocols for the follow-up of patients on AS were received from the 19 Cancer Networks which responded to the survey. Over half (57%) of the protocols recommended PSA testing at 3-monthly intervals initially for a period of between 12 and 24 months or until stable. Five (22%) recommended PSA testing at 4-monthly intervals initially for between 12 and 24 months. One (4%) protocol recommended PSA testing ≤ every 3 months for an initial period of 24 months; while one recommended testing between every 3-6 months, and another every 4-6 months.

Following the initial testing period of 12-24 months, 15 (65%) of the protocols recommend testing PSA at 6-monthly intervals thereafter though three (13%) specify 3-monthly if PSA is stable. One (4%) protocol recommended ongoing 3-monthly testing and one (4%) recommended ongoing 4-monthly testing. Eleven (48%) of the protocols specify a time period for the frequency of DRE testing of patients on active surveillance. In five (22%) of these DRE is recommended annually, in five (22%) DRE is recommended at the same frequency as PSA testing (3- or 4-monthly initially reducing to 6-monthly), and one (4%) recommended DRE testing 6-monthly.

There is greater variation in the frequency at which biopsy should be reconsidered; twenty of the protocols provided guidance in this area. Five (25%) recommended considering re-biopsy annually, three (15%) recommended considering re-biopsy at between 1 and 2 years, and two (10%) recommended re-biopsy at 1 year and at 2 years. One (5%) each of the remaining protocols recommended re-biopsy at ≤ 6 months; at 9 months and 2 years; at ≤ 1 year and at 2 years; at 1 year; at 1, 4 and 7 years; at 1 and 5 years; between 12 and 18 months; at 18 months and at 3 years; at 18 months then following clinical discretion; and at 2 and 5 years.

Two protocols also made a recommendation regarding measurement of PSA doubling time; one recommended measuring this at 6-monthly intervals (at the same frequency as PSA testing following the initial 3-monthly period). The other recommended measuring PSA

doubling time after 1 year of follow-up. One protocol also recommended undertaking MRI annually (alongside continuous 4-6 monthly PSA testing).

1.3.2 Surgery

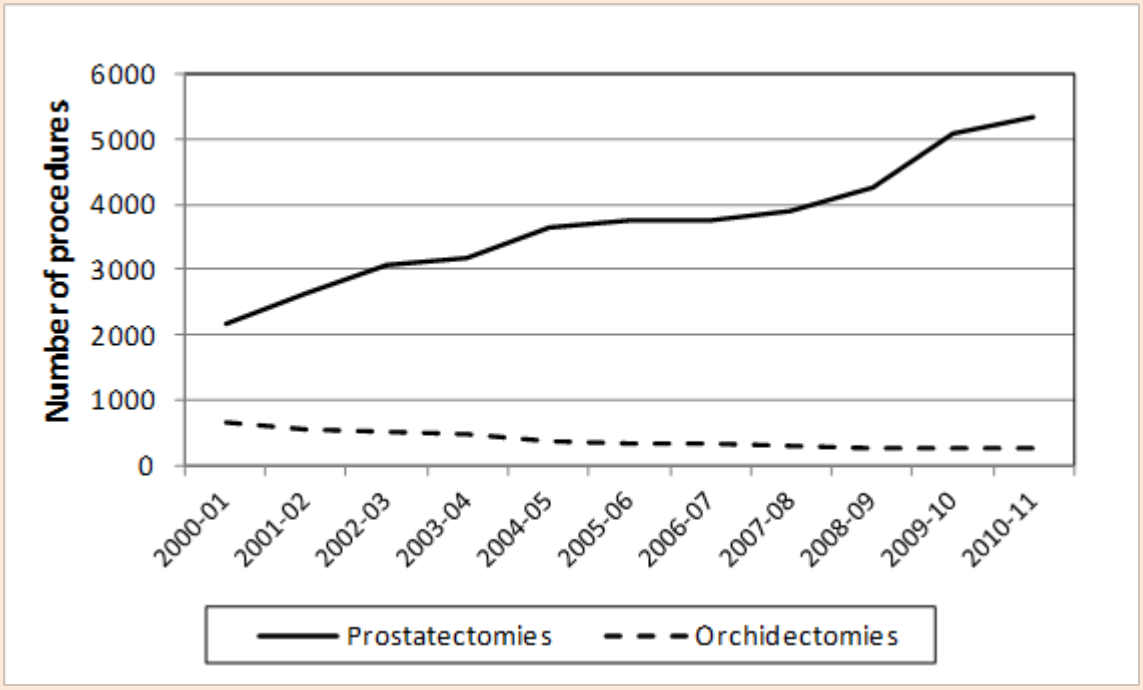
Total removal of the prostate, known as prostatectomy, is the primary curative surgical procedure for prostate cancer. Studies have reported significant reductions in deaths from prostate cancer and risk of metastases in those undergoing radical prostatectomy compared to AS or watchful waiting (Bill-Axelson *et al*. 2005). However, sometimes the tumour cannot be completely removed and disease can reccur.

The number of prostatectomies undertaken in England and Wales has more than doubled over the last 10 years, reaching 5,341 in 2010-11 (see Figure 38). The mean age at which prostatectomies were performed has remained at 63 years since 2003. Prostatectomies are most commonly performed in those aged between 60 and 74 years, with the proportion performed in this age group showing a slow increase from 65.4% in 2000 to 68.6% in 2011-12 (p=0.01). In contrast, prostatectomies performed on those aged 75+ years have decreased from 11.0% in 2000-01 to 2.4% in 2011-12 (p=0.001).

Of those reporting to the Radical Prostatectomy Dataset held by BAUS in 2011, most reported no previous treatment (62%), with 2% reporting previous management by TURP and 1% by radiotherapy (35% did not report this information) (BAUS 2012). The reason for undergoing prostatectomy was given in 72% of procedures reported; in 60% of procedures it was the primary treatment with 12% having undergone prior active surveillance. Salvage therapy was reported as the reason for prostatectomy in 0.5% of cases. Of those who had previously been on active surveillance, 43% were undergoing prostatectomy due to PSA progression, 17% due to clinical progression, and 13% due to Gleason progression. In 25% of cases it was the patient's decision to move from active surveillance to prostatectomy.

Update 2014

Figure 38: Number of prostatectomies and orchidectomies performed in England and Wales, 2000-2011 (source: HES; PEDW)



Surgical removal of the testes, known as orchidectomy, is sometimes used for the treatment of metastatic disease. Orchidectomy suppresses the level of testosterone in the body and

retards the growth of prostate tumours. However, the number of orchidectomies performed in England and Wales has decreased steadily over the last 10 years, from 645 in 2000-01 to 279 in 2010-11 ($p<0.001$). This is due to the increasing use of medical castration using hormonal therapy in place of surgical castration (see section 1.3.4). Orchidectomies are most commonly performed in those aged 75 years and over. However, there has been a slow increase in the proportion of patients undergoing orchidectomy who were aged less than 60 years, from 11.8% in 2000-01 to 22.9% in 2010-11 ($p<0.001$). This increase is reflected in a steady decrease in the proportion of patients who were aged 60-74 or 75+ years ($p<0.001$ and $p=0.03$ respectively).

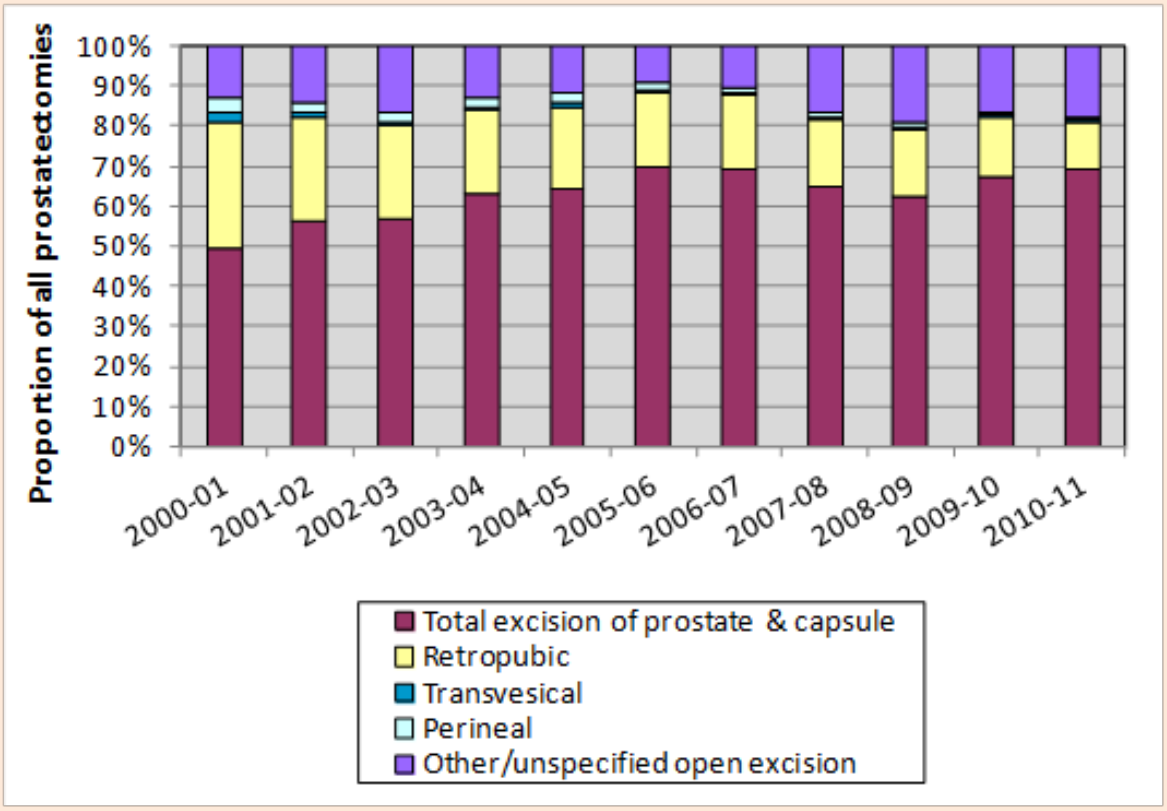
1.3.2.1 Prostatectomy by type

Of 2,163 prostatectomies reported voluntarily to the Radical Prostatectomy Dataset in 2011, 47% were laparoscopic, 17% were robotic, and 22% were open (15% did not report this information) (Bristish Association of Urological Surgeons 2012). Of the 992 laparoscopic procedures, 16 (2%) were converted to open procedures; reasons included failure to progress, haemorrhage, and adhesions.

Update 2014

However, these estimates differ from Hospital Episode Statistics (HES) data which show retropubic, transvesical and perineal to make up 11.9%, 0.3% and 0.8% of all prostatectomies performed in 2010-11 respectively (see Figure 39). All specified types of open excision have also decreased in frequency since 2000-01 ($p<0.05$). This data suggests that non-open procedures made up 69.1% of all prostatectomies in 2010-11. Laparoscopic prostatectomy can be recorded as either ‘total excision of prostate and capsule’ or ‘other specified open excision of prostate’ with additional codes. Therefore it was not possible to estimate the proportion of prostatectomies which were laparoscopic in nature. The former category represents the greatest proportion of prostatectomies in England and has increased significantly since 2000-01, reaching 69.1% in 2010-11 ($p=0.004$). However, NHS England reference cost data recorded 1816 laparoscopic/robotic procedures in the year 2009–10, suggesting that these options were used for 46% of all radical prostatectomies (Ramsay *et al*. 2012).

Figure 39: Proportion of prostatectomies undertaken in England by type, 2000-2011 (source: HES)



Update 2014

1.3.242 Prostatectomy by patient age group

The number of radical prostatectomies performed on prostate cancer patients has increased significantly since 1997 in all age groups ($p \leq 0.01$) (see Table 7). The number performed has risen fastest in those aged 45-69 years; in 2011-12 this group accounted for 86% of all prostatectomies performed. Once the size of the population in that age group is taken into account using the ASR, rates of prostatectomies have been consistently highest in those aged 65-69 years (see Table 8). The overall ASR of prostatectomy in England has increased from 50 in 1997-98 to 281 per 100,000 men diagnosed with prostate cancer in 2011-12.

Table 7: Number of prostatectomies (OPCS code M61) undertaken in men diagnosed with prostate cancer in England (source: HES)

Patient age	Financial year															Annual change
	1997 - 1998	1998 - 1999	1999 - 2000	2000 - 2001	2001 - 2002	2002 - 2003	2003 - 2004	2004 - 2005	2005 - 2006	2006 - 2007	2007 - 2008	2008 - 2009	2009 - 2010	2010 - 2011	2011- 2012	
0-44	2	3	2	5	5	15	11	11	14	17	16	21	25	35	31	+2
45-59	206	253	331	452	594	770	836	920	1049	977	967	1061	1314	1334	1442	+87
60-64	228	282	389	463	576	723	763	914	942	974	975	1152	1284	1365	1454	+86
65-69	235	323	411	477	683	785	885	920	979	906	922	1021	1340	1508	1564	+87
70-74	48	88	90	145	191	237	240	312	284	256	303	316	464	540	621	+35
75+	23	31	33	32	32	34	30	35	27	34	41	39	45	29	50	+1
Total	742	980	1256	1574	2081	2564	2765	3112	3295	3164	3224	3610	4472	4811	5162	+298

Table 8: Age standardised rate (ASR) of prostatectomies (OPCS code M61) undertaken in men diagnosed with prostate cancer in England per 100,000 men in England (source: HES)

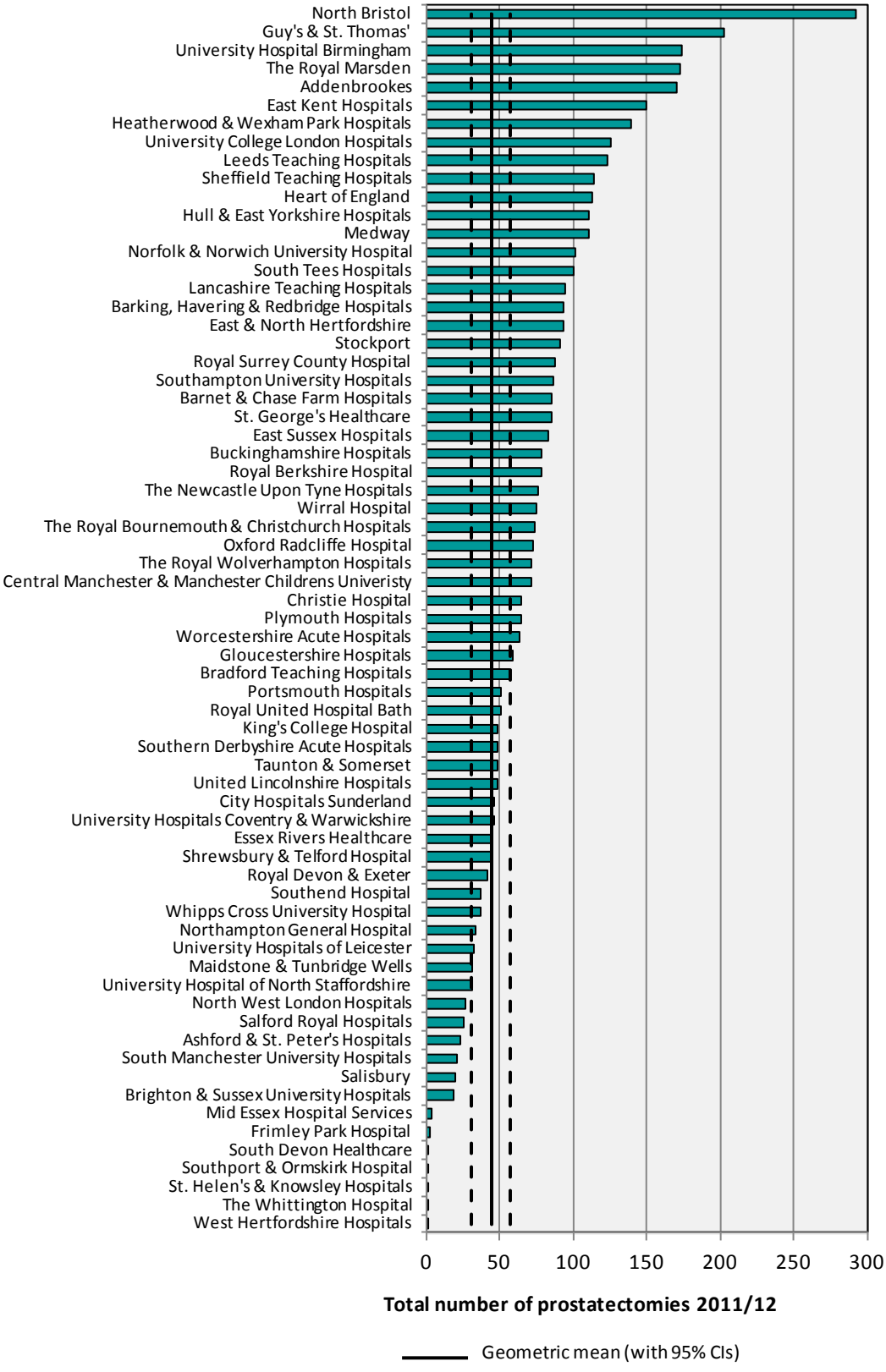
Patient age	Financial year														
	1997-1998	1998-1999	1999-2000	2000-2001	2001-2002	2002-2003	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008	2008-2009	2009-2010	2010-2011	2011-2012
0-44	0	0	0	1	1	2	1	1	2	2	2	2	3	4	4
45-59	79	94	120	159	201	244	253	273	307	286	295	337	425	440	475
60-64	316	385	525	617	764	944	965	1117	1123	1121	1053	1193	1305	1368	1457
65-69	353	486	622	721	1027	1161	1286	1312	1383	1274	1279	1371	1743	1906	1977
70-74	81	150	156	253	334	414	417	540	487	435	506	518	747	857	986
75+	41	52	54	51	50	53	46	51	36	42	48	43	47	29	50
Total	50	64	82	101	132	158	166	182	190	180	181	200	246	262	281

1.3.213 Prostatectomy by NHS Trust

The number of NHS Trusts in England performing prostatectomies on patients diagnosed with prostate cancer has decreased significantly in recent years, from 118 in 2002-03 to 67 in 2011-12 ($p<0.001$). In contrast the total number of prostatectomies being performed by the Trusts in this time period has more than doubled, from 2,565 in 2002-03 to 5,165 in 2011-12 ($p<0.001$). The geometric mean number of prostatectomies performed by an NHS Trust during 2011/12 was 44 (95% CI 31-57), however, the number performed by a Trust during 2011-12 ranged from one to 292 (see Figure 40).

Update 2014

Figure 40: Number of prostatectomies performed on patients diagnosed with prostate cancer by 67 NHS Trusts in England, 2011-12 (source: HES)



NHS Trust was unknown for 398 (8%) prostatectomies in 2011/12, therefore figures for some Trusts may be higher than depicted.

Update 2014

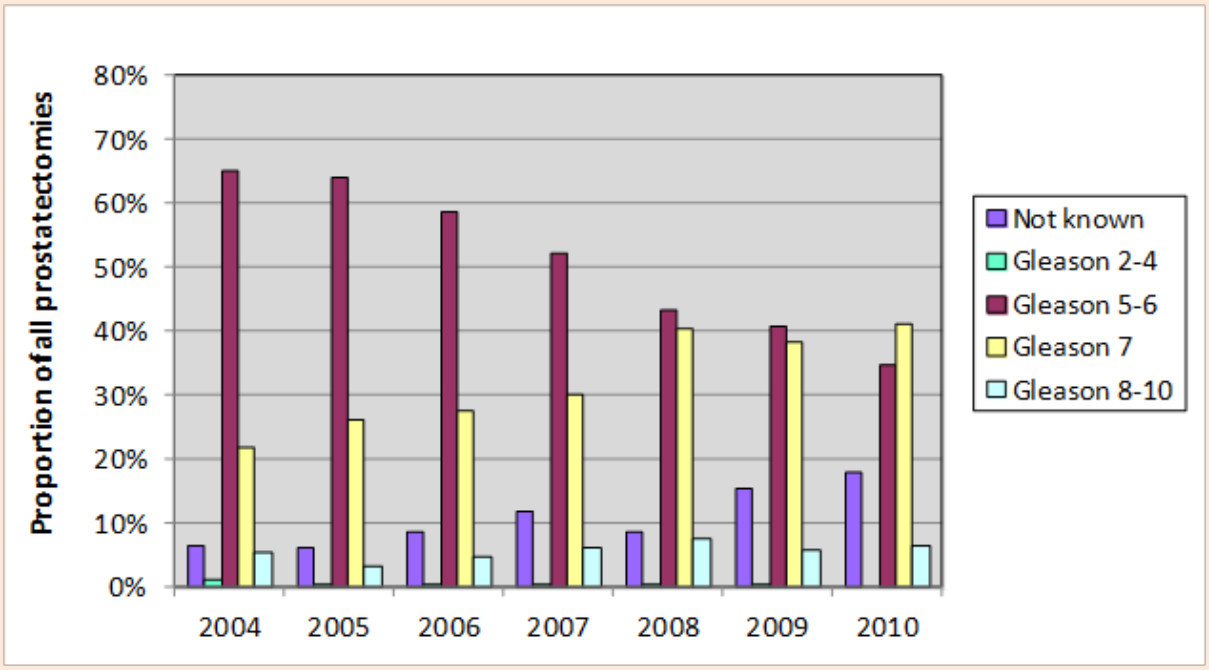
The NICE manual for improving outcomes in urological cancer, published in September 2002, states that ideally all radical prostatectomies undertaken in each network should be carried out by a single MDT and that radical prostatectomy should not be carried out by MDTs which carry out fewer than 50 radical operations per year (National Institute for Clinical Excellence 2002).

1.3.264 Prostatectomy by Gleason score

The British Association of Urological Surgeons (BAUS) collect data on prostatectomies undertaken and the Gleason score at diagnosis. However, reporting to BAUS is voluntary and the data only represent a subset of all prostatectomies undertaken in England and Wales. Since 2004 the number of prostatectomies reported to BAUS has varied between a third and half the number of all procedures recorded in HES. Figure 41 should therefore be interpreted with caution.

Prior to 2010 prostatectomies were most commonly reported to have been performed on patients with a Gleason score of 5-6 at diagnosis. However, the proportion of patients with this score has decreased steadily since 2004 ($p<0.001$), while the proportion of patients with a Gleason score of 7 at diagnosis has increased ($p=0.001$). In 2010, more patients with a Gleason score of 7 underwent prostatectomy than those with any other score. The proportion of reported prostatectomies whose Gleason score at diagnosis was unknown has increased from 6% in 2004 to 18% in 2010 ($p=0.004$).

Figure 41: Proportion of prostatectomies performed by Gleason score at diagnosis, 2004-2010 (source: BAUS)



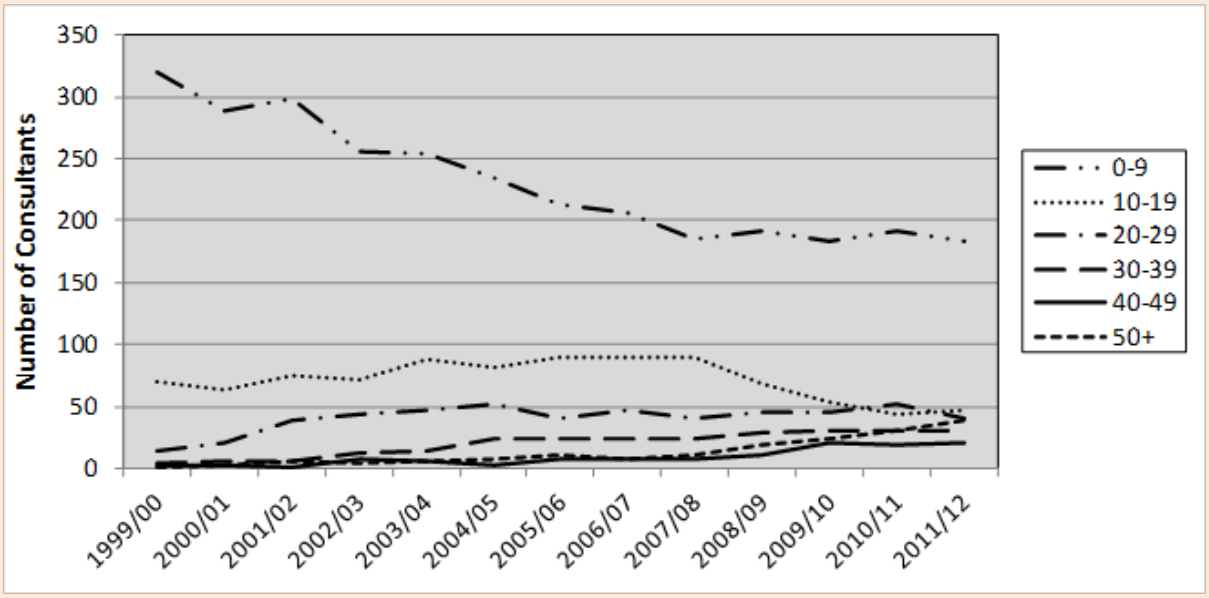
Update 2014

1.3.235 Prostatectomies performed per Consultant

There has been a significant decrease in the total number of Consultants performing prostatectomies on prostate cancer patients in England since 1999-00, decreasing from 411 to 358 in 2011-12 ($p<0.001$). In 2011-12, around half (51%) of all Consultants performed less than ten prostatectomies with 17% performing more than 40. This compares to 78% of all Consultants in 1999-00 performing less than ten prostatectomies and only 1% performing more than 40. Figure 42 shows the change in the number of consultants performing prostatectomies over time. There has been a significant decrease in the number of

consultants performing 0-9 prostatectomies (p<0.001) but a significant increase in the number of consultants performing 20-29, 30-39, 40-49 and 50+ (p≤0.02).]

Figure 42: Number of Consultants in England performing prostatectomies on patients diagnosed with prostate cancer, by number performed, 1999-2012 (source: HES)



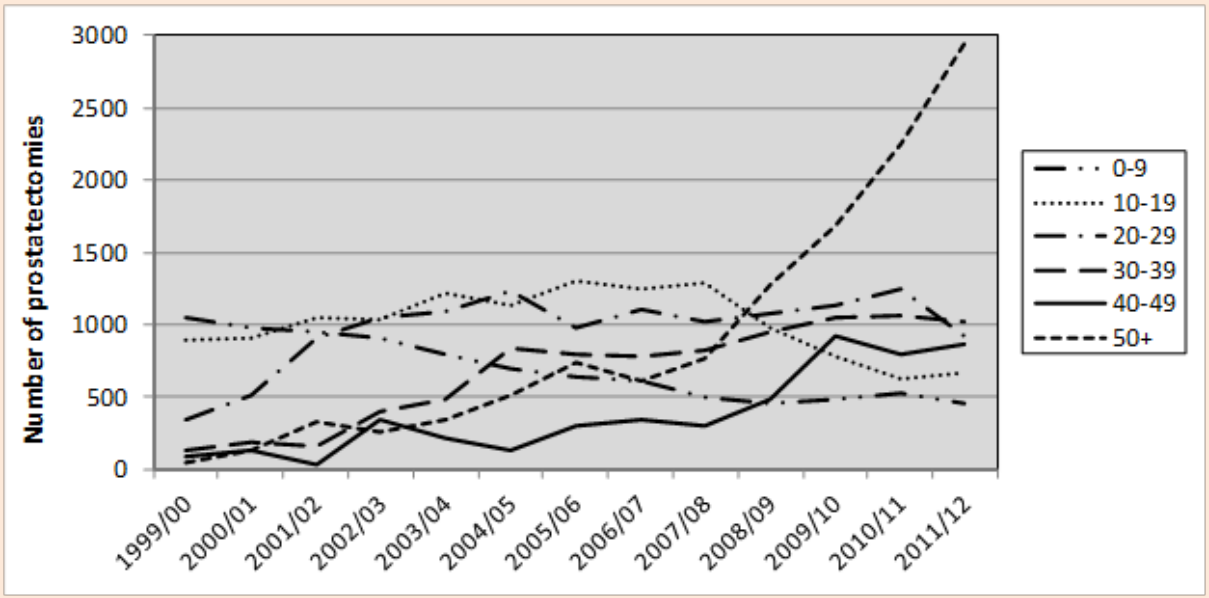
HES data records the code of the supervising Consultant for each surgical episode; this may not be the surgeon who performed the surgery.

Update 2014

During the same period there has been a significant increase in the total number of prostatectomies on prostate cancer patients in England since 1999-00, increasing from 2,554 to 6,866 in 2011-12 (p<0.001). In 2011-12, 43% of all prostatectomies were performed by a Consultant who undertook more than 50 per year, while only 7% were performed by Consultants who undertook less than ten per year. This compares to only 2% of prostatectomies being performed by Consultants who undertook more than 50 annually in 1999-00 and 41% being performed by Consultants who undertook less than ten annually.

Following the recommendation in 2002 that radical prostatectomy should not be carried out by MDTs which carry out fewer than 50 radical operations per year, surgeons carrying out fewer than five radical prostatectomies per year were required to refer patients to designated surgeons who were more specialised (National Institute for Clinical Excellence 2002). Figure 43 shows the change in the number of prostatectomies being performed by Consultants over time. There has been a significant decrease in the number of prostatectomies performed by Consultants who perform less than ten annually (p<0.001) but a significant increase in the number of prostatectomies performed by Consultants who perform 20 or more annually (p≤0.02).

Figure 43: Number of prostatectomies in England on patients diagnosed with prostate cancer, by number per Consultant, 1999-2012 (source: HES)



HES data records the code of the supervising Consultant for each surgical episode; this may not be the surgeon who performed the surgery.

Of 78 NHS Trusts reporting this information, 11 (14%) had an average of one prostatectomy per Consultant, six (8%) had an average of two prostatectomies per Consultant, 52 (67%) averaged more than 50 per Consultant, 27 (35%) averaged 100 or more per Consultant, and five (6%) performed an average of 200 or more per Consultant.

Update 2014

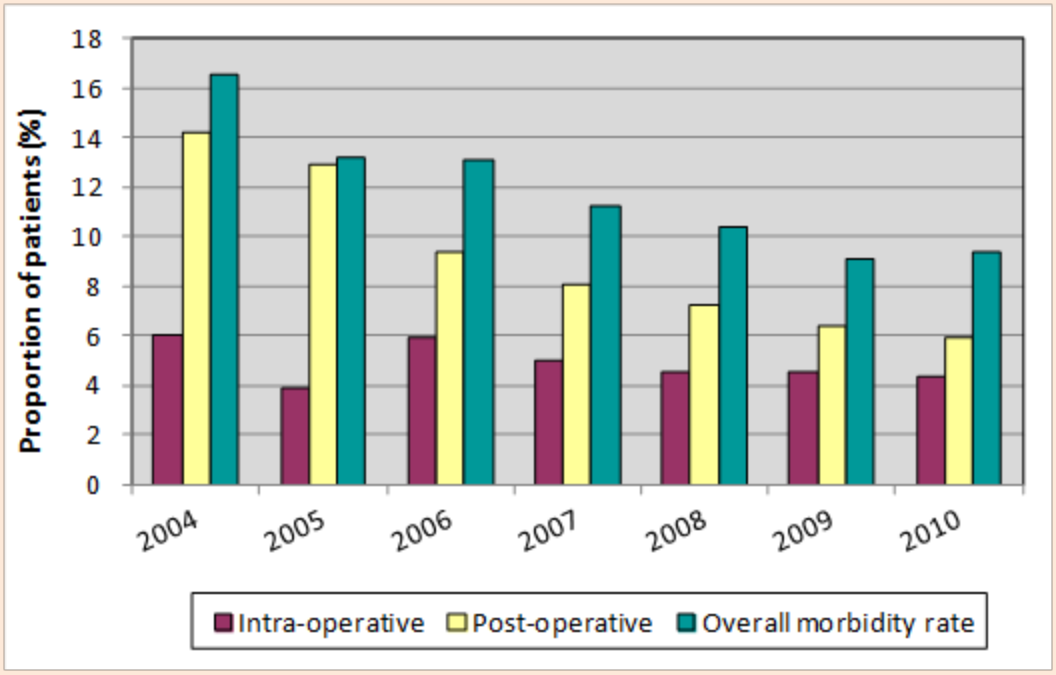
1.3.206 Treatment-related morbidity

Data voluntarily submitted to BAUS suggests a steady decrease in the overall morbidity rates associated with prostatectomy since 2004, with 9.4% of patients experiencing morbidity in 2010 (see Figure 44). However, this data represents only a small sample of prostatectomies undertaken in the UK and may be biased.

The proportion of patients experiencing post-operative complications has also decreased steadily since 2004, to 5.9% in 2010. This is due to a decrease in the proportion of patients experiencing leaks, wound infections, or ileus post-operatively. The proportion of patients experiencing intra-operative complications has remained at 4-5% since 2007. Where reported, these complications predominantly involved bleeding or rectal injury.

In 2010, 33% of intra-operative and 7% of post-operative complications delayed discharge of the patient, 35% and 5% required medical treatment, and 8% and 3% required surgery respectively. However, the significance of the complications was not reported in 14% and 73% of intra-and post-operative cases respectively. In no cases were the complications thought to contribute to the death of the patient.

Figure 44: Proportion of patients experiencing complications during or following prostatectomy, 2004-2010 (source: BAUS)



Update 2014

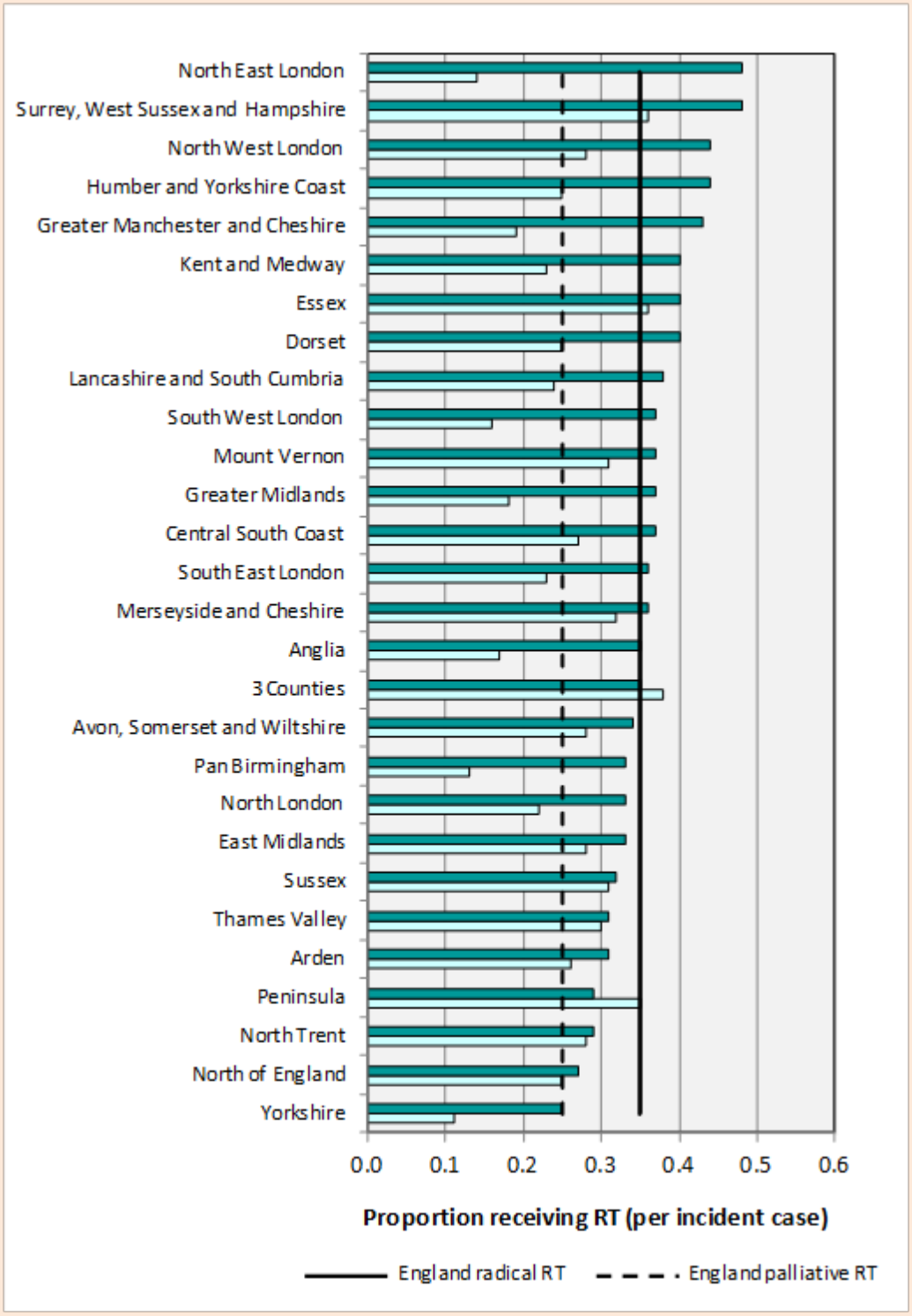
1.3.43 Radiotherapy

Radiotherapy can be delivered to the prostate in two ways; either using external x-ray beams from a linear accelerator or via brachytherapy where radiation sources are placed directly into the prostate gland. Since April 2009 it has become mandatory to submit a dataset for every patient receiving radiotherapy in the NHS in England. In 2011-12, 20,805 radiotherapy episodes were given to patients with a primary diagnosis of prostate cancer. This is an increase of 10% from the previous year and of 18% from 2009-10 (Ball 2012).

1.3.311 Radiotherapy by Cancer Network

Figure 45 shows the proportion of new cases of prostate cancer which received radiotherapy in 2010-11 in each of the Cancer Networks in England. On average 35% of newly diagnosed cases received radical radiotherapy in England and 25% received palliative radiotherapy. The highest proportion of newly diagnosed patients receiving radical radiotherapy was in North East London whilst the lowest was in Yorkshire (48% and 25% respectively). The highest proportion of newly diagnosed patients receiving palliative radiotherapy was in Three Counties and the lowest was again in Yorkshire (38% and 11% respectively). All Cancer Networks provided radical radiotherapy to a greater proportion of new cases than palliative, with the exception of Three Counties and the Peninsula who provided palliative radiotherapy to a greater proportion of new cases than radical radiotherapy (38% versus 35% and 35% versus 29% respectively).

Figure 45: Proportion of new cases of prostate cancer receiving radiotherapy (RT), 2010-2011 (source: RTDS – NATCANSAT)



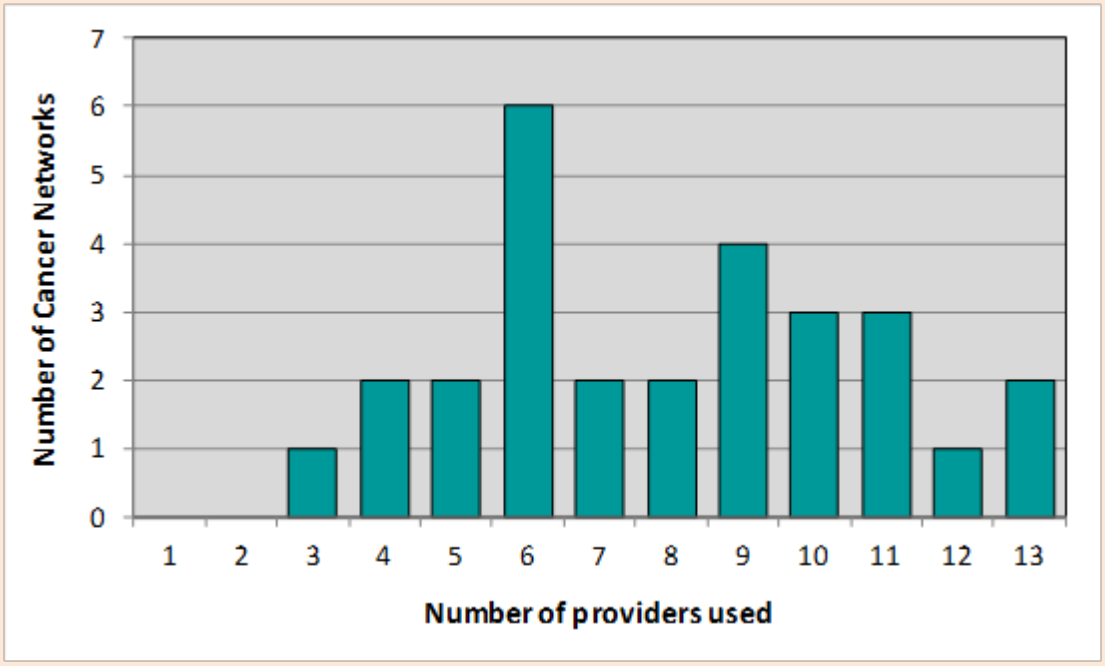
1.3.342 Radiotherapy by provider

During 2010-11 there were 49 providers of radiotherapy in England. Individual Cancer Networks used a median of eight providers (range 3 – 13) (see Figure 46). Of the 28 Cancer Networks, 14 (50%) used one main provider who undertook more than 80% of all treatment episodes, with between two and 12 other providers undertaking less than 20% each. Two (7%) Networks used one provider for 60-80% of all episodes and 7-10 other providers for less than 20% of treatment episodes. Eight (29%) of the Cancer Networks used between five

Update 2014

and 11 separate providers, each providing less than 60% of all episodes. Four (14%) Cancer Networks used between nine and 13 separate providers, each providing less than 40% of all episodes.

Figure 46: Number of providers used by Cancer Networks in England 2010-11 (source: RTDS – NATCANSAT)

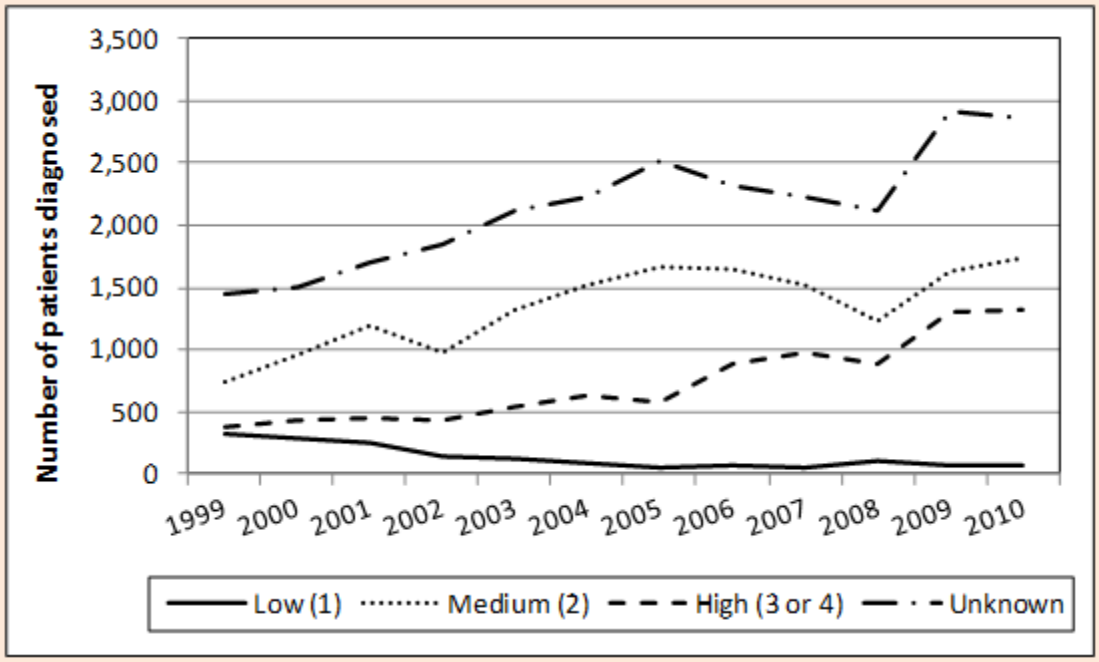


Update 2014

1.3.373 Radiotherapy by tumour grade

The tumour grade at radiotherapy is not reported for a large proportion of patients diagnosed with prostate cancer (47% to 55%; see Figure 47). The proportion which were low grade tumours at radiotherapy has decreased from 11% to 1% from 1999 to 2010. Those which were medium grade ranged between 25% and 35% over this time period. Those which were high grade tumours have increased from 13% to 22%. However, these figures should be interpreted with caution due to the high numbers of unknown grade.

Figure 47: Number of patients diagnosed with prostate cancer who received radiotherapy by grade of tumour, 1999-2010 (source: NCDR)



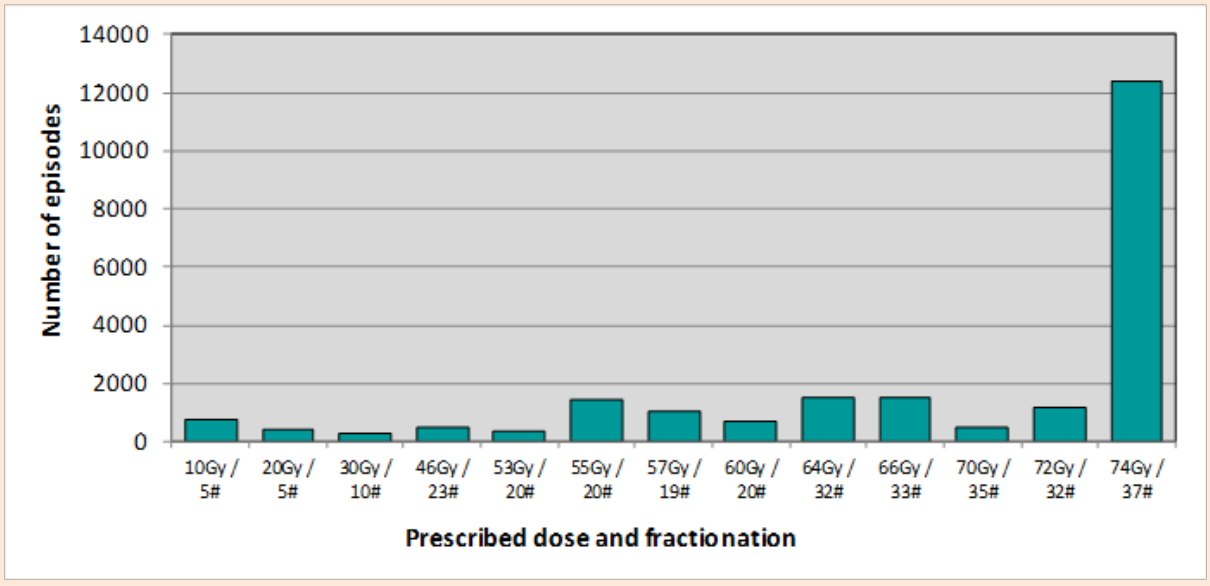
Tumour grade reflects the differentiation of cancer and normal cells within a sample of the tumour. This varies slightly from the Gleason grade which uses a different scale (1-5) and sums the two most common patterns in the sample. It is not possible to directly map between the two systems.

Update 2014

1.3.374 Variation in dose and fractionation

The most frequently prescribed dose fractionation for prostate cancer in England is 74 Gy in 37# (see Figure 48). This made up 63%, 59% and 67% of all prescribed dose fractionations in 2009-10, 2010-11 and 2011-12 respectively. Other fractionations schemes are likely to be part of closed or ongoing trials (Department of Health Cancer Policy Team 2012).

Figure 48: Radiotherapy episodes with a primary diagnosis of prostate cancer by prescribed dose and fractionation, April 2009 to March 2012 (source: RTDS - NATCANSAT)



1.3.315 Brachytherapy

Data suggests that 1.3% of men diagnosed with prostate cancer in 2009 were treated with brachytherapy (Bates *et al*. 1997). This represented 5.2% of all men who received some form of radiotherapy. There are two different radiation sources used in prostate cancer; low dose rate I125 seeds which are permanent implants to the prostate or high dose rate Ir192 temporary implants delivered using an after-loading machine. HES data show figures for low dose rate brachytherapy to have increased by 91% since first reported in 2006-07, reaching 1,174 procedures in 2010-11. In comparison, implantation of high dose rate brachytherapy was first reported in 2009-10 at 112 procedures. This increased to 142 procedures in 2010-11.

1.3.316 Combination external beam followed by HDR brachytherapy boost

Mandatory reporting of brachytherapy episodes to RTDS began in April 2011. The number of patients receiving external beam radiotherapy (EBRT) followed by a high dose rate (HDR) brachytherapy boost in England in 2011-12 is estimated to be 270, based on the number of patients receiving 37.5-38.0 Gy in 15 teletherapy episodes. However, this is thought to be an underestimate as it is difficult to predict the number of brachytherapy boosts delivered from patients in the higher fractionation (45-46 Gy) group and there is known under-reporting of brachytherapy in RTDS due to technical difficulties with nine providers. Also, only brachytherapy given with an automatic aftercare loading machine is captured by RTDS (Ball 2012).

In comparison, collection of the same data was begun through a National database in September 2010. For the fiscal year 2011-12 there were an estimated 323 HDR brachytherapy boosts given following EBRT. However, this is also thought to be an underestimate (Hoskins 2012).

Update 2014

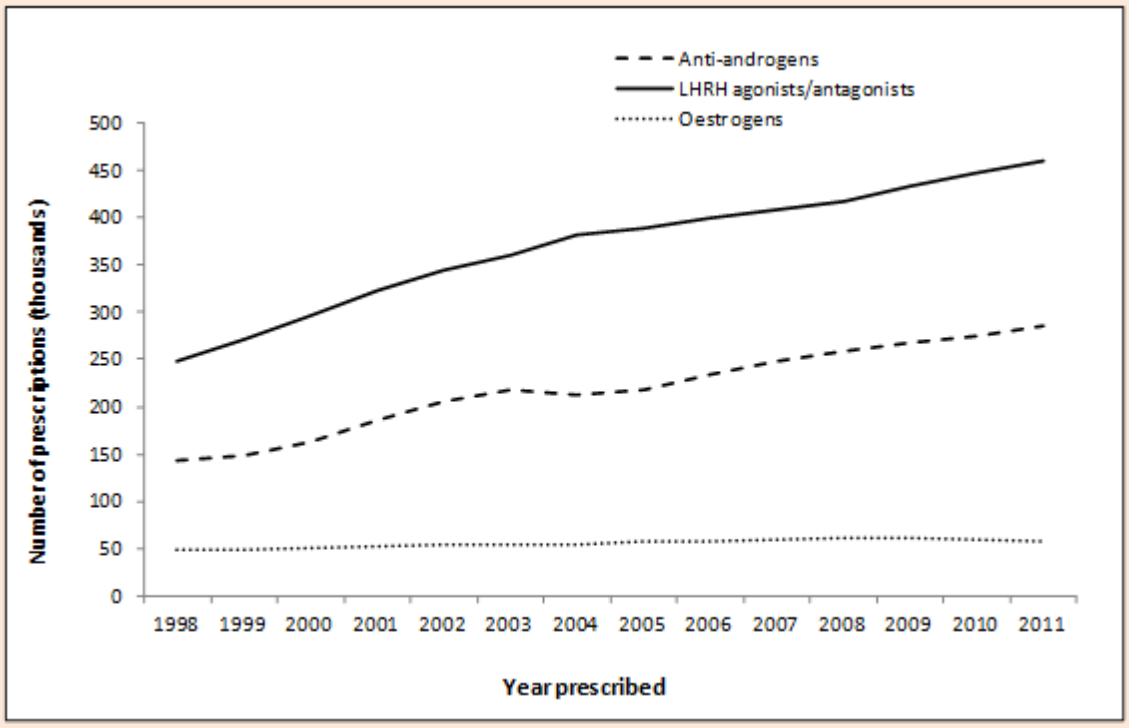
1.3.354 Androgen deprivation therapy

The function of androgen deprivation therapy (ADT) is to stop testosterone feeding prostate cancer and encouraging growth. Androgen suppression blocks the production of androgens including testosterone, with the aim of slowing the growth of prostate cancer cells. Most men who receive ADT for prostate cancer will receive the treatment for anything between a few months up to a few years (Bill-Axelson 2005). The Prostate Cancer Charity estimate that around 9,000 newly diagnosed men in the UK will receive ADT each year; around 26% of all new diagnoses (The Prostate Cancer Charity 2009). However, this does not include those men previously diagnosed who convert to ADT as their disease progresses or if their initial treatment is unsuccessful. It also does not include men who have been receiving ADT for several years. NICE clinical guidelines for prostate cancer recommend ADT as a treatment option for men with locally advanced and advanced (metastatic) prostate cancer, although it can also be offered to men with high risk localised disease (Bill-Axelson 2005). A survey conducted by The Prostate Cancer Charity found 43% of respondents had received ADT for localised disease, 33% for locally advanced, and 22% for advanced disease. Of all respondents, 73% were currently receiving ADT (The Prostate Cancer Charity 2009). GPs (53%) and practice nurses (40%) were most commonly cited as the healthcare professional involved in the provision of ADT.

Androgen blockade can be administered in one of three ways: (i) orchidectomy; (ii) injection of an LHRH agonist or antagonist; and (iii) oral anti-androgen or oestrogen tablets (which may also be used in combination with an orchidectomy or LHRH agonist). Data on the number of prescriptions for ADT for prostate cancer in England and Wales is not routinely collected. The Health and Social Care Information Centre (HSCIC) provides information on the number and cost of community-based prescriptions in England by drug but not details of the condition that they are being prescribed for.

Figure 49 shows the total numbers of prescriptions for ADT which are licensed for prostate cancer. These include a number of drugs which are also indicated for other conditions; therefore this is an overestimate and may be seen as an upper bound estimate. Only those prescriptions which were dispensed in England are included; this includes prescriptions written in Wales, Scotland, Northern Ireland and the Isle of Man but dispensed in England. It does not include prescriptions written in England but dispensed outside of England, items dispensed in hospital, or on private prescriptions.

Figure 49: Number of prescriptions for ADT in England, for treatments known to be used for prostate cancer, 1998-2011 (Data source: HSCIC)

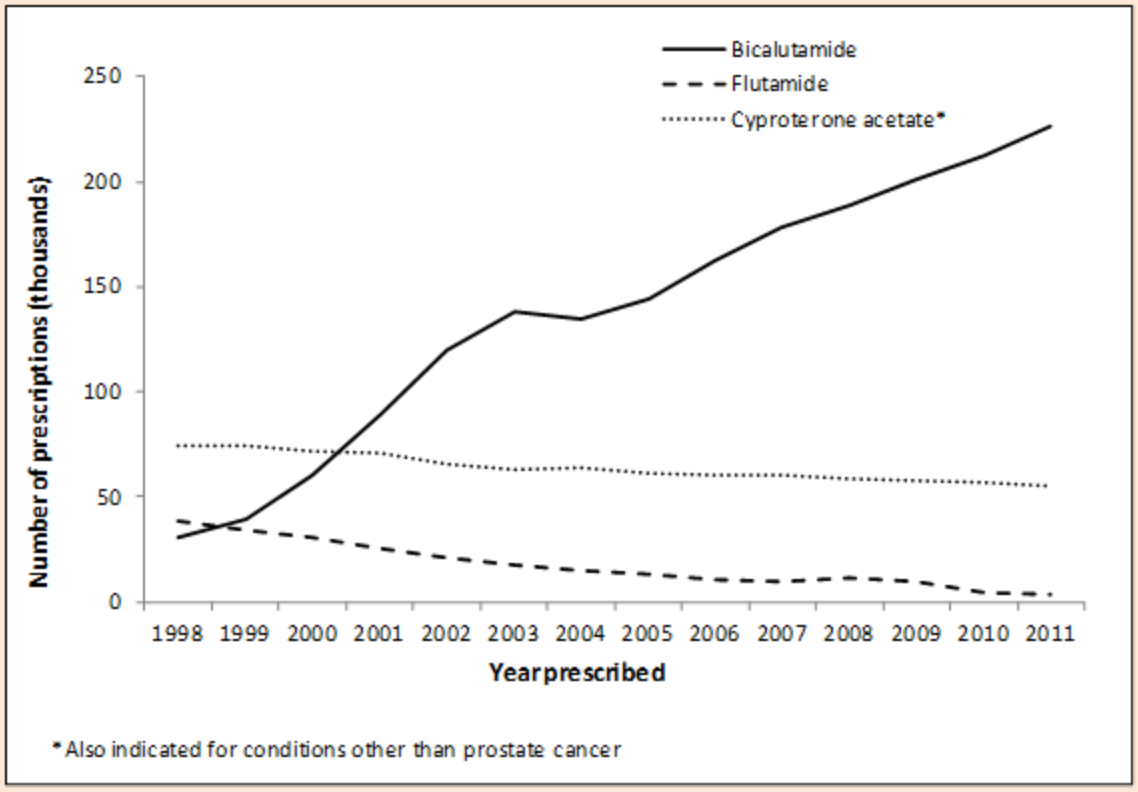


ADT prescriptions have continued to increase since 1998, with prescriptions of anti-androgens almost doubling from 143,900 in 1998 to 285,335 in 2011. LHRH agonists and antagonists have also shown a similar increase, from 248,600 in 1998 to 460,384 in 2011 (an increase of 85%). Anti-androgens and LHRH agonists were first introduced in 1984 and 1987 respectively and have shown almost continuous increases since. However, prescriptions of oestrogens maintained a relatively steady rate since 1998.

Bicalutamide and flutamide are only indicated for prostate cancer in the UK and therefore are representative of prescriptions for prostate cancer. Cyproterone acetate is also indicated for severe hypersexuality and sexual deviation, and for acne and hirsutism in women. The majority of the rise in anti-androgen prescriptions in recent years is due to the increased use of bicalutamide. Since it was introduced in 1994, bicalutamide has made up an increasing proportion of all anti-androgens prescribed, reaching 79% in 2011 (see Figure 50). Prescriptions of cyproterone acetate have fallen from a peak of over 85,000 per year in 1993 (National Collaborating Centre for Cancer 2008) to 55,550 in 2011 and now represent only 19% of anti-androgens indicated for prostate cancer. Prescriptions of flutamide have also fallen from a peak of around 40,000 prescriptions in 1996 (National Collaborating Centre for Cancer 2008) to less than 4,000 in 2011. Abiraterone acetate is also indicated for prostate cancer but none had yet been prescribed as of December 2011.

Update 2014

Figure 50: Number of anti-androgens prescribed for ADT in England, for treatments known to be used for prostate cancer, 1998-2011 (source: HSCIC)

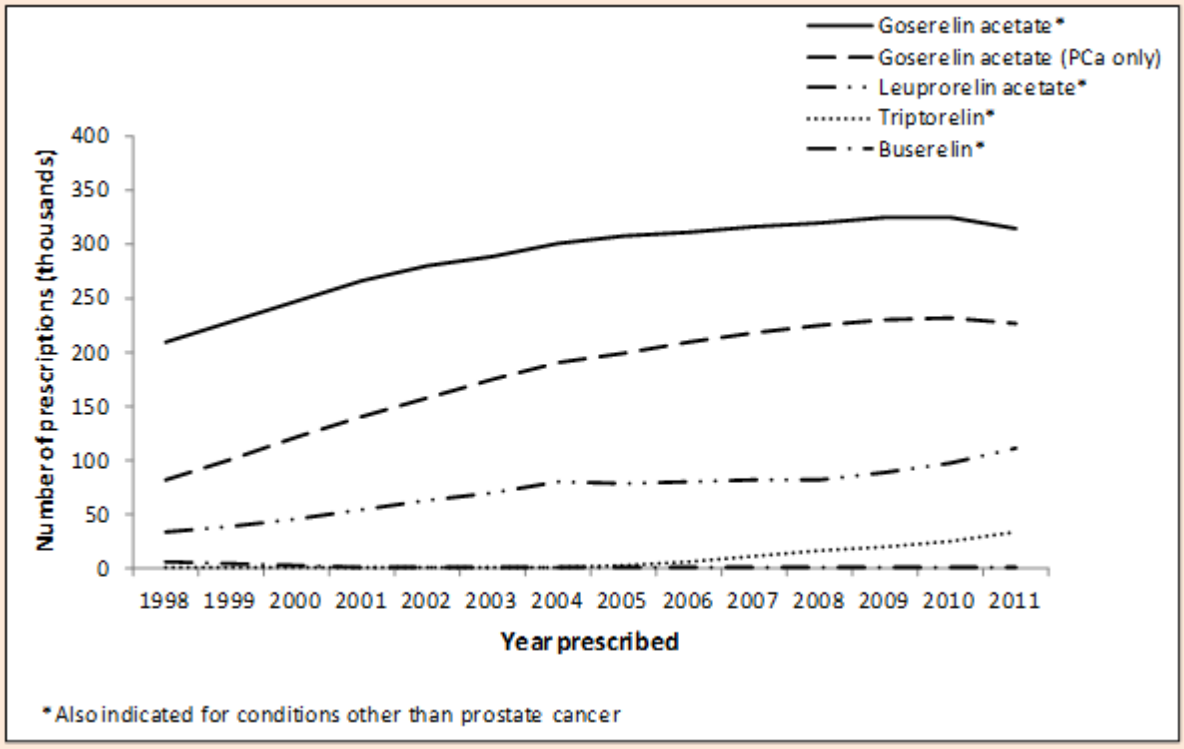


Update 2014

The majority of LHRH agonists indicated for prostate cancer are also prescribed for other conditions and figures are therefore an overestimate. For example, buserelin, goserelin acetate, leuprorelin acetate, and triptorelin are prescribed for other conditions including endometriosis, uterine fibroids, assisted reproduction, endometrial thinning, breast cancer, precocious puberty, and male hypersexuality with severe sexual deviation.

Goserelin acetate makes up the largest proportion of all LHRH agonists prescribed, though this has decreased from 84% of all LHRH agonists prescribed in 1998 to 68% in 2011. Some forms of goserelin acetate (Zoladex LA and Novgos) are known to be prescribed only for prostate cancer and these can be seen to make up a substantial proportion of the prescriptions (see Figure 51), leading the increasing trend. The proportion of goserelin acetate prescriptions which are known to be for prostate cancer increased from 39% in 1998 to 72% in 2011.

Figure 51: Number of LHRH agonists prescribed for ADT in England, for treatments known to be used for prostate cancer, 1998-2011 (source: HSCIC)



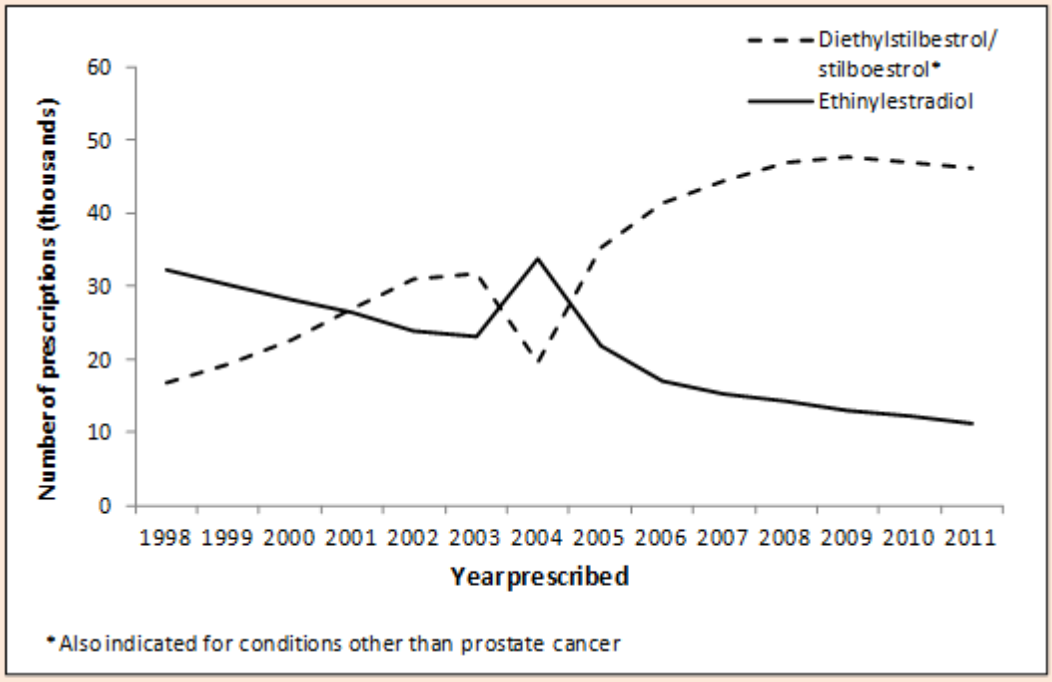
Update 2014

Degarelix and histrelin acetate were introduced in 2010, both of which are currently only prescribed for prostate cancer. Degarelix made up 0.3% of all LHRH agonists/antagonists in 2011, there were only 29 prescriptions for histrelin acetate in 2011 in total.

Of the two oestrogens prescribed for prostate cancer in the UK, diethylstilboestrol (previously stilboestrol) is also prescribed for breast cancer and figures are therefore an overestimate. However, ethinylestradiol in only indicated for prostate cancer in the UK. Prescriptions for diethylstilboestrol increased steadily from around 16,800 in 1998 to around 47,800 in 2009, but have begun to slightly decline since (see Figure 52). Prescriptions of ethinylestradiol have decreased steadily from around 32,200 in 1998 to around 11,300 in 2011. The exception to both these trends occurred in 2004, when prescriptions of diethylstilboestrol dropped dramatically and prescriptions of ethinylestradiol increased by a similar amount. This may have been linked to the renaming of stilboestrol to diethylstilboestrol that year.

Of the prescriptions for oestrogens which are indicated for prostate cancer, the proportion which were ethinylestradiol has decreased steadily from 68% in 1998 to 20% in 2011, with the exception of 2004 when it reached 63% of all prescriptions. In contrast, diethylstilboestrol has increased steadily from 34% to 80% of prescriptions, with the exception of 2004 when it dropped to 37%.

Figure 52: Number of oestrogen prescriptions in England, for treatments known to be used for prostate cancer, 1998-2011 (source: HSCIC)



Update 2014

1.3.41 Economic cost of ADT

Table 9 lists all androgen deprivation therapies indicated for prostate cancer in the British National Formulary (BNF), with the number of prescriptions and cost per prescription in 2011. Again, it is important to highlight the fact that many of these therapies are also indicated for other conditions, as shown in the table, and do not represent the cost associated with treating prostate cancer alone.

However, the largest cost in 2011 was for goserelin acetate in a form that is indicated for prostate cancer only (Novgos or Zoladex LA), estimated at around £53,400,000. The least spent on a LHRH agonist in 2011 was for buserelin (around £7,049). Of the anti-androgens indicated for prostate cancer, bicalutamide prescriptions proved the most expensive in 2011 (around £3,200,000), all of which were for prostate cancer patients (as bicalutamide is not currently indicated for other treatment).

Table 9: Androgen deprivation therapy licensed for prostate cancer in England and Wales; number of prescriptions in England in 2011 and associated cost

Drug class	Chemical name	Indicated for	Indications other than prostate cancer	Items (prescriptions)	Net ingredient cost (NIC)	NIC per item
Anti-androgen	Bicalutamide	(i) Locally-advanced at high risk of progression (alone or adjuvant to RT or orchidectomy); (ii) locally-advanced non-metastatic if other intervention inappropriate; (iii) advanced in combination with gonadorelin analogue or orchidectomy	-	225,825	£3,168,970	£14.03
	Cyproterone acetate	(i) prevention of flare with initial gonadorelin analogue; (ii) long-term palliative where gonoadorelin analogue or orchidectomy not suitable; (iii) hot flushes with gonadorelin analogue or after orchidectomy	Severe hypersexuality & sexual deviation; acne & hirsutism in women	54,215	£1,624,401	£29.96
	Flutamide	Advanced disease	-	3,959	£134,218	£33.90
	Abiraterone acetate	Metastatic, castration-resistant disease which has progressed (in combination with prednisone or prednisolone), during or after chemotherapy	-	0	-	-
LHRH agonist	Buserelin	Advanced disease	Endometriosis; assisted reproduction	130	£7,049	£54.22
	Goserelin acetate (Zoladex)	(i) Locally-advanced (alternative to orchidectomy); (ii) neoadjuvant to RT or prostatectomy in high-risk localised or locally advanced disease; (iii) metastatic disease	Breast cancer; endometriosis; endometrial thinning; uterine fibroids; assisted reproduction	88,100	£5,941,648	£67.44
	(Novgos & Zoladex)		-	226,430	£53,400,953	£235.84
	Histrelin acetate	Advanced disease	-	29	£28,710	£990.00
	Leuprorelin acetate	(i) Locally advanced (alternative to orchidectomy); (ii) adjuvant to RT or prostatectomy in high-risk localised or locally advanced disease; (iii) metastatic disease	Endometriosis; endometrial thinning; uterine fibroids	111,312	£20,543,297	£184.56

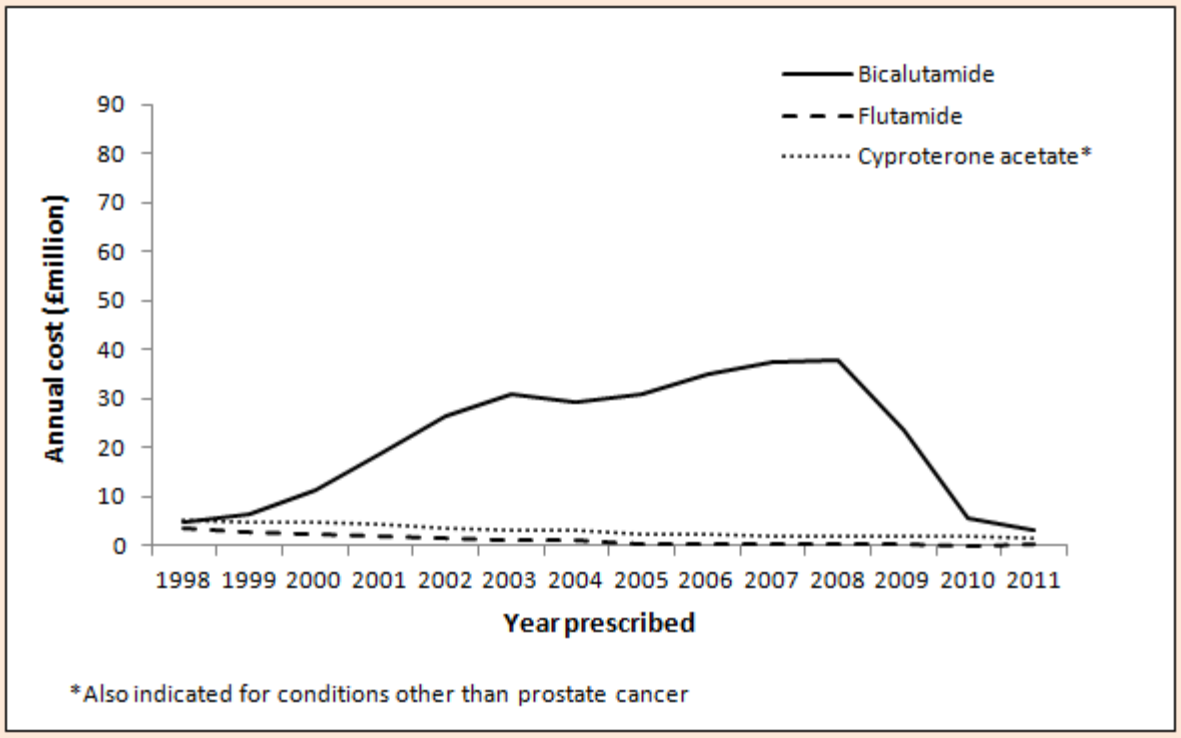
Drug class	Chemical name	Indicated for	Indications other than prostate cancer	Items (prescriptions)	Net ingredient cost (NIC)	NIC per item
	Triptorelin acetate	Prostate cancer	Endometriosis; precocious puberty; uterine fibroids; male hyper-sexuality with severe sexual deviation	31,661	£5,240,374	£165.52
	Triptorelin embonate			250	£103,500	£414.00
LHRH antagonist	Degarelix	Advanced, hormone-dependent disease	-	1,550	£218,068	£140.69
Oestrogen	Diethylstilbestrol	Prostate cancer (but not first-line due to side effects)	Breast cancer	46,313	£3,702,612	£79.95
	Ethinylestradiol		-	11,303	£1,958,465	£173.27

Update 2014

1 RT = radiotherapy;

The annual cost of anti-androgen prescriptions for prostate cancer has decreased rapidly in the last few years (see Figure 53). This is primarily due to a rapid decline in the cost of bicalutamide prescriptions since its peak in 2008.

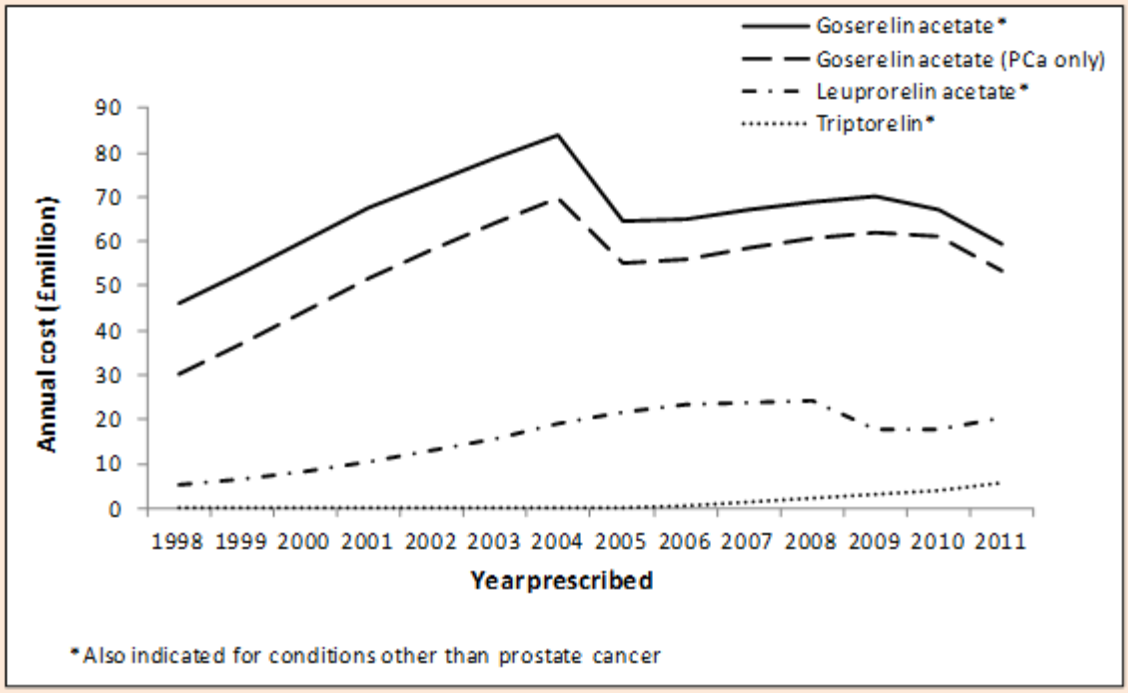
Figure 53: Annual cost of anti-androgen prescriptions in England, for treatments known to be used for prostate cancer (source: HSCIC)



Update 2014

The annual cost of goserelin acetate prescriptions has also seen a decline since its peak in 2004. Though goserelin acetate is also indicated for a number of other conditions, including breast cancer, formulations which are indicated only for prostate cancer (Zoladex LA and Novgos) make up the majority of the cost each year and lead this trend (see Figure 54). Leuprorelin acetate and triptorelin historically have a much lower annual cost than goserelin but appear to be increasing in cost. However, these medications are also indicated for other conditions (such as endometriosis and uterine fibroids) which may contribute to this rise. Prescriptions for the remaining LHRH agonists and antagonists which are indicated for prostate cancer (buserelin, histrelin acetate, and degarelix) have never reached an annual cost over £0.5 million. The annual cost of prescriptions for buserelin has decreased from around £299,600 in 1998 to around £7,049 in 2011. Degarelix and histrelin acetate were both first prescribed in 2010 and cost around £218,000 and £29,000 in 2011 respectively.

Figure 54: Annual cost of LHRH agonist prescriptions in England, for treatments known to be used for prostate cancer (source: HSCIC)



1.3.4.2 Treatment-related morbidity

Update 2014

In a survey conducted by The Prostate Cancer Charity in 2009, the most common side effects experienced by men undergoing ADT for prostate cancer were hot flushes (85%), erectile dysfunction (83%), loss of libido (80%), and fatigue (71%) (The Prostate Cancer Charity 2009). The most common effects experienced on the mental health of men with prostate cancer were cognitive effects (47%), becoming more emotional (43%), and mood swings (39%). Other potential physical side effects are breast tenderness, weight gain, muscle loss, and osteoporosis (McLeod *et al*. 1997; Isbarn *et al*. 2009; Eastham 2007). There may also be an increased risk of developing diabetes and heart disease (Smith 2007; Hakimian *et al*. 2008).

However, adverse events associated with ADT vary by the type of therapy given. Orchidectomy and LHRH agonists are commonly associated with erectile dysfunction (in around 70% of men), hot flushes (in 55-80% of men), and loss of sexual desire (in around 50% of men) (Mulhall 2009; Higano 2003; Potosky *et al*. 2001). While around half of men taking anti-androgen therapy are thought to develop gynecomastia to some degree (McLeod *et al*. 1997).

1.3.4.3 Hormone-relapsed prostate cancer

Hormone-relapsed prostate cancer (HRPC) is defined by disease progression despite traditional androgen deprivation therapy with a serum testosterone level < 0.7 nmol/l. Current approved licensed drugs for management of HRPC recommended by NICE include docetaxel and more recently abiraterone acetate. Docetaxel in combination with prednisolone is considered first line treatment for HRPC with an improvement in median survival of 2.4 when compared to the previous gold standard, mitoxantrone (Tannock *et al*. 2004). A newer generation taxane, cabazitaxel, has been licensed by the FDA but not approved by NICE (National Institute for Health and Clinical Excellence 2013) for use in HRPC that has previously been treated with a docetaxel-containing regime (FDA Centre for Drug Evaluation and Research Approval Package for: Jevtana 2010). A head-to-head trial (FIRSTANA) comparing docetaxel with cabazitaxel is due for completion in 2014.

Second line treatment after docetaxel-containing chemotherapy failure is limited to abiraterone acetate. Abiraterone acetate is an inhibitor of androgen biosynthesis which blocks androgen synthesis in the adrenal glands in addition to the testes. Abiraterone acetate, which was approved by NICE in May 2012, used in combination with prednisolone is recommended as an option for HRPC if the disease has progressed after one docetaxel-containing chemotherapy regimen. Abiraterone acetate with prednisolone offers a median survival benefit of 4.6 months when compared to prednisolone alone (Fizazi *et al*. 2012).

Drug development for HRPC is a fast growing field with many phase III trials due for completion in the next few years for novel agents such as enzalutamide and Radium 223 chloride. Denosumab used for preventing bone metastases in HRPC is currently under NICE review.

1.3.5 Other treatments

High intensity focused ultrasound (HIFU) consists of focused ultrasound waves emitted from a transducer, which cause tissue damage by mechanical and thermal effects as well as by cavitation. The goal of HIFU is to heat malignant tissues above 65°C so that they are destroyed by coagulative necrosis (Glaser *et al*. 2013). Figures for high intensity focused ultrasound treatment of the prostate were first reported by HES in 2007-08, since then they have varied between 168 and 216 procedures per year.

Another potential treatment for prostate cancer is cryotherapy; this involves passing cold gases through needles into the prostate to destroy the gland. HIFU and cryotherapy are not currently recommended for men with localised prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions (Bates *et al*. 1997).

Update 2014

1.4 References

Ball C (RTDS, NatCanSAT), personal communication, 20th September 2012.

Bates TS *et al*. A comparison of endorectal magnetic resonance imaging and transrectal ultrasonography in the local staging of prostate cancer with histopathological correlation. British Journal of Urology 1997; 79(6): 927-93234

Bechis *et al*. Impact of age at diagnosis on prostate cancer treatment and survival. Journal of Clinical Oncology 2011; 29(2): 235-241

Ben-Shlomo Y *et al*. The risk of prostate cancer amongst black men in the United Kingdom: The PROCESS cohort study. Eur Urol 2008; 53(1): 99-105

Bill-Axelson A *et al*. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005; 352: 1977–84

Bratt O. Hereditary prostate cancer: clinical aspects. J Urol 2002; 168(3): 906-913

Bray F *et al*. Prostate cancer incidence and mortality trends in 37 European countries: An overview. European Journal of Cancer 2010; 46: 3040-3052

Brewster DH *et al*. Rising incidence of prostate cancer in Scotland: increased risk or increased detection? BJU Int 2000; 85(4): 463-72

British Association of Urological Surgeons. Analyses of Radical Prostatectomy Dataset: January 1st – December 31st 2011. June 2012. Available online at: http://www.baus.org.uk/Resources/BAUS/Documents/PDF%20Documents/Data%20and%20Audit/Prostatectomy%20Analyses%202011.pdf

Cancer Research UK. Statistics and outlook for prostate cancer. Updated 24 July 2012. Available online at: http://www.cancerresearchuk.org/cancer-help/type/prostate-cancer/treatment/statistics-and-outlook-for-prostate-cancer

Carter BS *et al*. Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA 1992; 89(8): 3367-3371

Cormio *et al*. Prostate cancer detection rates in different biopsy schemes. Which cores for which patients? World J Urol 2012; Epub ahead of print: DOI 10.1007/s00345-012-0989-8

Department of Health Cancer Policy Team. Radiotherapy in England 2012. Available online at: https://www.wp.dh.gov.uk/publications/files/2012/11/Radiotherapy-Services-in-England-2012.pdf (accessed 16th January 2013)

Djavan B *et al*. Prostate biopsy: who, how and when. An update. Can J Urol 2005; 12(Suppl 1): 44–48

Eastham JA. Bone health in men receiving androgen deprivation therapy for prostate cancer. J Urol 2007; 177(1): 17-24

Edwards SM *et al*. Two percent of men with early-onset prostate cancer harbor germline mutations in the BRCA2 gene. Am J Hum Genet 2003; 72(1): 1-12

Eichler K *et al*. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol 2006; 175: 1605–1612

Elo JP, Visakorpi T. Molecular genetics of prostate cancer. Ann Med 2001; 33(2): 130-141

Epstein JI. Gleason score 2-4 adenocarcinoma of the prostate on needle biopsy: a diagnosis that should not be made. Am J Surg Path 2000; 24: 477-478

Evans HS *et al*. Recent trends in prostate cancer incidence and mortality in Southeast England. European Urology 2003; 43: 337-341

European Association of Urology. Guidelines on Prostate Cancer. January 2011. Available online at: http://www.uroweb.org/gls/pdf/08%20Prostate%20Cancer_LR%20March%2013th%202012.pdf

FDA Center for Drug Evaluation and Research Approval Package for: Jevtana. June 17, 2010. Available online at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201023s000Approv.pdf; accessed 11th January 2013

Fizazi K *et al*. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012; 13(10): 983-992

Fourcade R *et al*. Treatment costs of prostate cancer in the first year after diagnosis: a short-term cost of illness study for France, Germany, Italy, Spain and the UK. BJU International 2009; 105: 49-56

Glaser A *et al*. Patient-reported outcomes of cancer survivors in England 1-5 years after diagnosis: a cross-sectional survey. BMJ Open 2013; 3: e002317

Guichard G *et al*. Extended 21-sample needle biopsy protocol for diagnosis of prostate cancer in 1000 consecutive patients. Eur Urol 2007; 52: 430–435

Haidinger G *et al*. The prevalence of lower urinary tract symptoms in Austrian males and associations with sociodemographic variables. Eur J Epidemiol 1999; 15: 717–22

Hakimian P *et al*. Metabolic and cardiovascular effects of androgen deprivation therapy. BJU Int 2008; 102(11): 1509-1514

Hara R *et al*. Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. Urology 2008; 71(2): 191-5

Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. Urology 2003; 61(2 Suppl. 1): 32-38

Hoskins P (Prostate Cancer Guideline Development Group, NICE), personal communication, 21st September 2012.

International Union Against Cancer. TNM Classification of Malignant Tumours. 7th Edition, Wiley-Blackwell 2009.

Jemal A *et al*. Cancer statistics, 2009. Ca Cancer J Clin 2009; 59: 225-249

Isbarn *et al*. Androgen deprivation therapy for the treatment of prostate cancer: consider both benefits and risks. Eur Urol 2009; 55(1): 62-75

Johns LE, Houlston RS. A systematic review and meta-analysis of familial prostate cancer risk. BJU Int 2003; 91(9): 789-794

Jones JS *et al*. Saturation technique does not improve cancer detection as an initial prostate biopsy strategy. J Urol 2006; 175: 485–488

Kolonel LN *et al*. The multiethnic cohort study: exploring genes, lifestyle and cancer risk. Nat Rev Cancer 2004; 4(7): 519-527

Lujan M *et al*. Prostate cancer detection and tumor characteristics in men with multiple biopsy sessions. Prostate Cancer Prostatic Dis 2004; 7: 238–242

Lyratzopolous G *et al*. Socio-demographic inequalities in stage of cancer diagnosis: evidence from patients with female breast, lung, colon, rectal, prostate, renal, bladder, melanoma, ovarian and endometrial cancer. Annals of Oncology 2013; 24: 843-850

Maddams J *et al*. Projections of cancer prevalence in the United Kingdom, 2010-2040. British Journal of Cancer 2012; 107: 1195-1202

McLeod *et al*. Combined androgen blockage: the gold standard for metastatic prostate cancer. Eur Urol 1997; 32(suppl. 3): 70-77

Melia *et al*. Rates of prostate-specific antigen testing in general practice in England and Wales in asymptomatic and symptomatic patients: a cross-sectional study BJU International 2004; 94: 51-56

Metcalfe C *et al*. The risk of prostate cancer amongst South Asian men in southern England: the PROCESS cohort study. BJU Int 2008; 102(10): 1407-1412

Mian BM *et al*. Predictors of cancer in repeat extended multisite prostate biopsy in men with previous negative extended multisite biopsy. Urology 2002; 60: 836–840

Mistry M *et al*. Cancer incidence in the United Kingdom: projections to the year 2030. British Journal of Cancer 2011; 105: 1795-1803

Mokete M *et al*. The increased rate of prostate specific antigen testing has not affected prostate cancer presentation in an inner city population in the UK. BJU Int 2006; 97: 266–269

Mulhall JP. Defining and reporting erectile dysfunction outcomes after radical prostatectomy: challenges and misconceptions. J Urol 2009; 181(2): 462-71

National Cancer Intelligence Network. Cancer incidence and survival by major ethnic group, England, 2002-2006. June 2009. Available online at: http://publications.cancerresearchuk.org/downloads/product/CS_REPORT_INCSURV_ETHNIC.pdf

National Cancer Intelligence Network. Mortality from prostate cancer: Urological cancers SSCRG. 2012. Available online at: www.ncin.org.uk/view.aspx?rid=1701

National Cancer Intelligence Network. Treatment routes in prostate cancer. South West Public Health Observatory 2012. Available online at: www.ncin.org.uk/view.aspx?rid=1260

National Institute for Health and Clinical Exellence. Prostate Cancer: Diagnosis and treatment. February 2008. Available online at: http://www.nice.org.uk/nicemedia/live/11924/39687/39687.pdf

National Collaborating Centre for Cancer. Prostate Cancer: diagnosis and treatment – An assessment of need. February 2008. Available online at: http://guidance.nice.org.uk/CG58/NeedsAssessment/pdf/English

National End of Life Care Intelligence Network. Deaths from urological cancers in England, 2001-2010. October 2012.

National Institute for Clinical Excellence. Improving outcomes in urological cancers: The Manual. September 2002. Available online at: http://www.nice.org.uk/nicemedia/pdf/Urological_Manual.pdf (accessed 27th February 2013)

National Institute for Health and Clinical Excellence. Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. May 2012. Available online at: http://www.nice.org.uk/nicemedia/live/13731/59186/59186.pdf; accessed 11th January 2013

NHS Cancer Screening Programmes. Prostate cancer risk management programme; 2010. Available online at: www.cancerscreening.nhs.uk/prostate/publications.html (accessed December 2012).

Norberg M *et al*. The sextant protocol for ultrasound-guided core biopsies of the prostate underestimates the presence of cancer. Urology 1997; 50: 562–566

Oesterling JE *et al*. Influence of patient age on the serum PSA concentration. An important clinical observation. Urol Clin North Am 1993; 20: 671–680

Office for National Statistics. Cancer Atlas of the UK and Ireland 1991-2000. Chapter 2, page 9. Available online at http://www.ons.gov.uk/ons/search/index.html?newquery=Cancer+Atlas+of+the+United+Kingdom+and+Ireland+1991-2000

Office for National Statistics (2002) Report: Results of the ICD-10 bridge coding study, England and Wales, 1999. Health Statistics Quarterly 14: 75-83.

Office for National Statistics (2003) Mortality statistics cause Review of the Registrar General on deaths by cause, sex and age, in England and Wales, 2001. Annex I, Series DH2, no.28.

Office for National Statistics. Cancer survival in England – patients diagnosed 2005-2009 and followed up to 2010. Available online at: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-239726 (accessed 27th February 2013)

Pashayan N *et al*. Excess cases of prostate cancer and estimated over-diagnosis associated with PSA testing in East Anglia. Br J Cancer 2006; 95: 401–5

Update 2014

Prostate Cancer Risk Management Programme. First survey of Prostate Specific Antigen Services in England. Available online at http://www.cancerscreening.nhs.uk/prostate/survey-prostate-specific-antigen-services.pdf (accessed 2012)

Prostate Cancer Risk Management Programme. Second survey of Prostate Specific Antigen Services in England. Available online at http://www.cancerscreening.nhs.uk/prostate/second-survey-psa-tests.pdf (accessed 2012)

Patel AR, Klein EA. Risk factors for prostate cancer. Nat Clin Pract Urol 2009; 6(2): 87-95

Pepe P, Aragona F. Saturation prostate needle biopsy and prostate cancer detection at initial and repeat evaluation. Urology 2007; 70: 1131–1135

Potosky AL *et al*. Impact of screening on incidence and mortality of prostate cancer in the United States. Epidemiol Rev 2001; 23(1): 181-186

Quinn M, Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons. BJU Int 2002; 90: 162-173

Ramsay C *et al*. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health Technol Assess 2012; 16(41)

Rohrmann S *et al*. Family history of prostate cancer and obesity in relation to high-grade disease and extraprostatic extension in young men with prostate cancer. Prostate 2003; 55(2): 140-146

Sanchez-Chapado M *et al*. Comparison of digital rectal examination, transrectal ultrasonography, and multicoil magnetic resonance imaging for preoperative evaluation of prostate cancer. European Urology 1997; 32(2): 140-149

Sant M *et al*. EUROCARE-4: Survival of cancer patients diagnosed in 1995-1999. Results and commentary. European Journal of Cancer 2009; 45: 931-991

Scattoni V *et al*. Biopsy schemes with the fewest cores for detecting 95% of the prostate cancers detected by a 24-core biopsy. Eur Urol 2010; 57: 1–8

Smith MR. Androgen deprivation therapy for prostate cancer: new concepts and concerns. Curr Opin Endocrinol Diabetes Obes 2007; 14(3): 247-254

Takenaka A *et al*. A prospective randomized comparison of diagnostic efficiency between transperineal and transrectal 12-core prostate biopsy. Prostate Cancer and Prostatic Diseases 2008; 11: 134-8

Tannock IF *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351(15): 1502-1512

The Prostate Cancer Charity. Hampered by Hormones? Addressing the needs of men with prostate cancer. June 2009. Available online at: http://prostatecanceruk.org/hormones

The Prostate Cancer Charity. Screening for prostate cancer and the PSA test. Available online at: http://prostatecanceruk.org/media/36688/policy_pos_screening_aug2009_full.pdf

Thompson D, Easton DF. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002; 94(18): 1358-1365

UK NEQAS. http://www.ukneqas.org.uk/content/Pageserver.asp

University of Liverpool (2003) Towards a Consensus Protocol on Prostate Biopsies: Indications, Techniques and Assessment. Conference Report p21. 6th June 2003. Available at http://www.cancerscreening.nhs.uk/prostate/conference-report.pdf

Update 2014

1

2 Williams *et al*. Prostate-specific antigen testing rates remain low in UK general practice: a
3 cross-sectional study in six English cities. BJU International 2011; 108: 1402-1408

4 Zaridze DG *et al*. International trends in prostatic cancer. Int J Cancer 1984; 33(2): 223-30

Update 2014

2 1 Communication and support

2.1 2 Introduction

3 Information and care should be centred on the needs of individual men as they arise from
4 prostate cancer or its treatment, as well as the needs of their partners and carers.

5 Many of the basic communication and patient care needs of men with prostate cancer are
6 addressed in other guidance on urological cancers and palliative care from The National
7 Institute for Health and Clinical Excellence (NICE 2002; 2004), The Welsh Assembly
8 Government (2005) and The Department of Health (2004a; 2004b)

9 This previous published guidance from NICE and DH identifies many communication and
10 information needs which apply to men with prostate cancer. There is evidence from the
11 National Audit Office (2005a; 2005b) that these recommendations remain relevant, but have
12 been particularly poorly implemented in this group though the recent National Cancer Patient
13 Experience Surveys have shown some improvements (Department of Health 2010 and
14 2012).

15 The information needs of men with prostate cancer include:

16 • basic anatomy and pathology to enable men and their carers to understand how prostate
17 cancer might affect them
18 • aims, risks and likely effects of proposed diagnostic procedures
19 • the likely range of impact and rate of progression of prostate cancer
20 • potential treatment options, including the probability of improved survival or symptom
21 reduction. This needs to convey known benefits, uncertainties about benefits, known risks
22 and potential short and long-term adverse effects
23 • reasons why a man might decide to opt for or not opt for radical treatment, whether
24 provisionally or for the long term
25 • the effect which treatment for prostate cancer may have on a man's quality of life,
26 including his relationship with his partner
27 • reasons for not offering interventions which men might expect
28 • urological, oncological, radiological, palliative care and other relevant services
29 • other sources of information, possible self help action and sources of support.

30 A significant number of older men have prostate cancer and many of their needs have been
31 identified and addressed in the standards of the ‘National Service Framework for Older
32 People’ (Department of Health 2001).

33 Men’s support needs are known to differ from women’s. Men appear to see support mainly in
34 terms of good information. Although men are reluctant to access support services, this may
35 depend on factors such as age. Some men welcome counselling. However there are
36 indications that men prefer support groups, not so much for emotional support, but to impart
37 and receive information.

38 Partners are perceived as the main care-giver and may experience more distress than men
39 with prostate cancer. Partners are known to be eager to help in the decision making process,
40 but at the same time this is also known to lead to panic and an inability to search for
41 information.

2.2 Communicating with men with prostate cancer, their partners and carers

This section focuses particularly on the way in which specific information is communicated and how men's ability to make decisions about their treatment options may be enhanced and their choices facilitated.

Diagnosis, staging or treatment of a man with prostate cancer requires consideration at the outset of how adequate information and communication between the man and the teams looking after him is to be achieved.

Members of the urological cancer multidisciplinary team (MDT) are responsible for communicating specialist information to men with prostate cancer and are required to identify a "'key worker' for each individual patient" (Department of Health 2004a). All men will require a range of information about their disease and its treatment but their communication needs and preferences will differ, depending on individual factors such as age and cultural and ethnic background.

As men's priorities, needs and concerns change, so does their need for appropriate information. It is unlikely that a single source or form of information is enough to meet all these needs at all stages. Effective communication and information sharing is therefore a continuing responsive, adaptive process.

There are a range of communication methods available that help create the 'well informed man', (and his informal carers) although it is uncertain from the evidence how much time it takes and there is little consensus on specific resources. Written and verbal interventions, group seminars, audio tape and telephone interventions, video and other multimedia methods, and support groups are all useful interventions. Materials most favourably reviewed in the literature will periodically need updating. Incomplete or incomprehensible information impairs patient experience, outcomes and satisfaction. The evidence shows that risks, benefits, side effects and clear comparisons of different treatment options are often not well explained in information resources.

Some treatment options confront men with choices which they find particularly difficult and many men appreciate information given through some form of 'expert system', which enables them to focus on the issues most relevant to their values and wishes, and to bypass information about issues which are of less importance to them. The importance of shared decision making, incorporating the individual values and attitudes of men with prostate cancer in the choice of care and treatment, was identified in the NICE Guidance on 'Improving outcomes in urological cancers' (NICE 2002).

There is considerable variation in the amount and type of information needed to make a treatment decision, particularly in localised prostate cancer, and little agreement on the need for most individual items. Thus there is a risk that, the treatment decisions which each man makes when there is a choice between different management options may be more a reflection of the information he has been offered than of his personal values and wishes.

Recommendation	**Follow the recommendations on communication and patient-centred care in the NICE cancer service guidance Improving outcomes in urological cancers and Improving supportive and palliative care for adults with cancer throughout the patient journey. [2008]**
Qualifying statement	This recommendation is based on consensus of the GDG and supported by the NAO report and the findings of cancer peer review in England which shows that patient centred care measures are less often complied with in urological cancer teams than in teams managing other cancer sites.

Recommendations	**Offer men with prostate cancer individualised information tailored to their own needs. This information should be given by a healthcare professional (for example, a consultant or specialist nurse) and may be supported by written and visual media (for example, slide sets or DVDs). [2008]** **Offer men with prostate cancer advice on how to access information and support from websites, local and national cancer information services, and from cancer support groups. [2008]** **Before choosing or recommending information resources for men with prostate cancer, check that their content is clear, reliable and up-to-date. Seek feedback from men with prostate cancer and their carers to identify the highest quality information resources. [2008]** **Ascertain the extent to which the man wishes to be involved in decision making and ensure that he has sufficient information to do so. [2008]**
Qualifying statement	There was GDG consensus in support of these recommendations, based on evidence of unmet need.

Clinical evidence (2008)

Evidence from a systematic review (Echlin, 2002) indicates that if provided with detailed, up to date and broad information about prostate cancer men gain substantial knowledge about their disease and the management of it. There was little evidence about how informational provision affects a man's satisfaction with his treatment choice. The information provided to men varies in quality: the evidence suggests that although high quality information is available it is often outweighed by the greater quantity of low quality material.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

2.3 Decision support

Since both the nature of the disease and the benefits of treatment may be uncertain, decision making in prostate cancer treatment is complex. In view of this complexity, there is growing interest in, and awareness of, structured decision aids for men considering prostate cancer treatments. Such aids may be of particular use in helping men who have localised prostate cancer or are considering hormonal therapy.

Decision aids are evidence based tools designed to be delivered by appropriately trained professionals to support and enable people to participate in decisions about their healthcare by:

- making explicit the existence and nature of the specific choices facing the individual patient
- providing specific, individualised information to help each patient understand the nature and probable risks, benefits and outcomes of their treatment options (see Chapter 4 for recommendations on nomograms)
- guiding the patient through each step in making a decision, taking into account an individuals beliefs and values.

Such aids are not a substitute for a comprehensive communication process with men and their families.

Recommendation	**Use a validated, up-to-date decision aid[c] in all urological cancer multidisciplinary teams (MDTs). Healthcare professionals trained in its use should offer it to men with localised prostate cancer when making treatment decisions. [2008]**
Qualifying statement	This recommendation was based on a combination of high quality evidence and GDG consensus.

Clinical evidence (2008)

Evidence about the effectiveness of decision aids comes from a systematic review of randomised trials in a range of conditions, including localised prostate cancer (O'Connor *et al*. 2003), and from observational studies (Brink *et al*. 2000; Feldman-Stewart *et al*. 2001; Feldman-Stewart *et al*. 2004; Holmes-Rovner *et al*. 2005; Schapira *et al*. 1997). Knowledge of disease and treatment options and participation in the decision process were increased with decision aids, but there was no evidence of an effect on satisfaction with decisions, anxiety, or health outcomes.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Recommendation	**Discuss all relevant management options recommended in this guideline with men with prostate cancer and their partners or carers, irrespective of whether they are available through local services. [2008]**
Qualifying statement	This recommendation is based on GDG consensus alone.

2.4 Specific problems

Management of prostate cancer carries a number of specific challenges in communication, arising from uncertainty over treatment benefits, potential for a profound impact from treatment-related adverse events and the often extended course of the disease.

Radical treatment of prostate cancer carries the threat of significant disturbance to quality of life and functioning. The development of incontinence, bowel toxicity and temporary or permanent damage to sexual function and enjoyment are all recognised as possible sequelae of prostate cancer treatments and are addressed in Chapter 4. For some men the prospect of these effects may be less acceptable than the disease itself – especially when there is uncertainty about whether prostate cancer is a threat to their longer term survival. Decisions about treatment options rely on men being sufficiently well informed at each stage of their illness to understand the choices they face and with sufficient time to consider the options carefully.

Recommendation	**Ensure that mechanisms are in place to allow men with prostate cancer and their primary care providers to gain access to specialist services throughout the course of their disease. [2008]**
Qualifying statement	This recommendation is based on GDG consensus alone.

2.4.1 Prostate cancer and the effect it may have on men's sense of masculinity

Being diagnosed with cancer and the specific nature and side effects of many of the treatments used in prostate cancer can have an effect on a man's sense of masculinity. This

c A decision aid for men with localised prostate cancer is available from NHS Shared decision making.

will apply to factors such as sexual function, urinary problems, bowel function, pain, fatigue and psychological distress. This impact on 'masculinity' is not, in general, a focus of attention in prostate cancer research. However by assessing it in the context of men's accounts and theoretical considerations, it is possible to conclude that the impact of this aspect of prostate cancer may be profound for men. The effects of having prostate cancer will also, in some circumstances, depend on variables that include stage of disease and treatment received. These issues are discussed in more detail in Appendix A of the evidence review.

While there is a paucity of work that would illuminate how information received and decision making impacts on masculinity or vice versa, some men will not trade quality for quantity and may wish to forgo the 'best' treatment from the healthcare professional's perspective: rather they would prefer to keep their potency for example. There is evidence to suggest that men who have been treated with hormonal therapies, retrospectively regret that treatment decision.

Little is known about the issues surrounding masculinity in ethnic minority groups and the impact prostate cancer may have on homosexual men.

Recommendations	**Adequately inform men with prostate cancer and their partners or carers about the effects of prostate cancer and the treatment options on their sexual function, physical appearance, continence and other aspects of masculinity. Support men and their partners or carers in making treatment decisions, taking into account the effects on quality of life as well as survival. [2008]** **Offer men with prostate cancer and their partners or carers the opportunity to talk to a healthcare professional experienced in dealing with psychosexual issues at any stage of the illness and its treatment. [2008]**
Qualifying statement	These recommendations are based on qualitative evidence and GDG consensus.

Clinical evidence (2008)

Manne and co-workers (Manne *et al*. 2004) reported that the effects of a structured group psychosocial intervention were modest and psychological distress was not affected. Another study (Thornton *et al*. 2004) reported partial support for the effectiveness of a single-session communication intervention on patient social/family wellbeing and partners' general stress.

Researchers were unable to define the concept of masculinity well enough to enable a literature search. The GDG commissioned an expert position paper on this topic (see Appendix A of the evidence review).

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Research recommendation	**More research should be undertaken into the sense of loss of masculinity in men receiving treatment for prostate cancer [2008].**
Why this is important	Treatments used in prostate cancer may affect on a man's sense of masculinity (sexual function, urinary problems, bowel function, pain, fatigue and psychological distress) but, as this has not been a focus of attention in research, there is a paucity of information to aid decision making for men and their partners.

2.5 References

Brink SG, Birney AJ & McFarren AE (2000) Charting your course: formative evaluation of a prostate cancer treatment decision aid. International Electronic Journal of Health Education, 2000 Jan 1; 3: 44–54.

Department of Health (2012) Second National Cancer Patient Experience Survey. London: Department of Health.

Department of Health (2010) National Cancer Patient Experience Survey Programme - 2010: national survey report. London: Department of Health.

Department of Health (2004a) Manual for Cancer Services 2004. London: Department of Health.

Department of Health (2004b) The NHS Cancer Plan and the new NHS: Providing a patient-centred service. London: Department of Health.

Department of Health (2001) National Service Framework for Older People: Modern standards and service models. London: Department of Health.

Echlin KN & Rees CE (2002) Information needs and information-seeking behaviors of men with prostate cancer and their partners: a review of the literature Cancer Nursing 25(1): 35–41.

Feldman-Stewart D, Brundage MD & Van ML (2001) A decision aid for men with early stage prostate cancer: theoretical basis and a test by surrogate patients. Health Expectations, 4: 221–234.

Feldman-Stewart D, Brundage MD, Van ML & Svenson O (2004) Patient-focussed decision-making in early-stage prostate cancer: insights from a cognitively based decision aid. Health Expectations, 2004 Jun; 7: 126–141.

Holmes-Rovner M, Stableford S, Fagerlin A, Wei JT, Dunn RL, Ohene-Frempong J, Kelly-Blake K & Rovner DR (2005) Evidence-based patient choice: a prostate cancer decision aid in plain language. BMC Medical Informatics & Decision Making, 5: 16.

Manne S, Babb J, Pinover W, Horwitz E, Ebbert J (2004) Psychoeducational group intervention for wives of men with prostate cancer. Psycho oncology 13: 37–46.

National Audit Office (2005a) Tackling Cancer: Improving the patient journey. London: National Audit Office. National Audit Office (2005b) The NHS Cancer Plan: a progress report. London: National Audit Office.

National Institute for Clinical Excellence (2002) Improving Outcomes in Urological Cancers. NICE cancer service guidance. London: National Institute for Clinical Excellence.

National Institute for Clinical Excellence (2004) Improving Supportive and Palliative Care for Adults with Cancer. NICE cancer service guidance. London: National Institute for Clinical Excellence.

O'Connor AM, Stacey D, Rovner D, Holmes-Rovner M, Tetroe J, Llewellyn-Thomas H, Entwistle V, Rostom A, Fiset V, Barry M & Jones J (2003) Decision aids for people facing health treatment or screening decisions.[update in Cochrane Database Syst Rev.2003;(2):CD001431; PMID: 12804407]. [Review] [152 refs]. Cochrane Database of Systematic Reviews, CD001431.

Schapira MM, Meade C & Nattinger AB (1997) Enhanced decision-making: the use of a videotape decision-aid for patients with prostate cancer. Patient Educ.Couns., 1997 Feb; 30: 119–127.

1 Thornton AA, Perez MA & Meyerowitz BE (2004) Patient and partner quality of life and
2 psychosocial adjustment following radical prostatectomy. Journal of Clinical Psychology in
3 Medical Settings, 11: 15–30.

4 Welsh Assembly Government (2005) Wales National Cancer Standards. Wales: Welsh
5 Assembly Government. Available from
6 http://www.wales.nhs.uk/sites3/Documents/983/Urology_Eng.pdf

3 Diagnosis and staging of prostate cancer

3.1 When to biopsy

Men who are ultimately diagnosed with prostate cancer usually present in primary care with no clear symptoms of the disease. NICE has issued guidance to GPs on the referral of men who are suspected of having prostate cancer (NICE clinical guideline 27, 2005). Asymptomatic men may also request a PSA test as covered by the Prostate Cancer Risk Management Programme (PCRMP). This section assumes that men have had a digital rectal examination (DRE) and usually a prostate specific antigen (PSA)[d] test. Prostate cancer may also be diagnosed as a result of investigation of, or treatment for, benign prostatic hyperplasia (BPH). BPH is associated with a higher level of PSA, which may lead to a suspicion of prostate cancer, and biopsy of tissue resected during a trans-urethral resection of the prostate (TURP) may result in a diagnosis of prostate cancer.

The aim of prostate biopsy is actually to detect those prostate cancers with the potential for causing harm. A significant proportion of asymptomatic men in whom prostate cancer is detected by prostate biopsy following PSA measurement do not require active treatment. Men with clinically insignificant prostate cancers that were destined never to cause any symptoms, or affect their life expectancy, may not benefit from knowing that they have the 'disease'. Indeed, the detection of clinically insignificant prostate cancer should be regarded as an (under-recognised) adverse effect of biopsy.

In order to identify men who are most suitable for prostate biopsy, there is a need to identify a group at risk, not just of prostate cancer, but of significant prostate cancer. Factors associated with significant prostate cancer are: PSA level, Gleason score, smaller prostate volume, abnormal DRE findings, age, and black African and black Caribbean ethnicity, whereas a previous negative prostate biopsy reduces this risk. These factors have been incorporated into predictive models, based on North American data, that allow an individualised assessment of the risk of high grade disease on biopsy. The chance of finding higher grade prostate cancer on biopsy is not related to the presence or absence of lower urinary tract symptoms.

Recommendations	**To help men decide whether to have a prostate biopsy, discuss with them their prostate-specific antigen (PSA) level, digital rectal examination (DRE) findings (including an estimate of prostate size) and comorbidities, together with their risk factors (including increasing age and black African or black Caribbean ethnicity) and any history of a previous negative prostate biopsy. Do not automatically offer a prostate biopsy on the basis of serum PSA level alone. [2008]** **Give men and their partners or carers information, support and adequate time to decide whether or not they wish to undergo prostate biopsy. Include an explanation of the risks (including the increased chance of having to live with the diagnosis of clinically insignificant prostate cancer) and benefits of prostate biopsy. [2008]**
Qualifying statement	These recommendations are based on evidence from well designed North American observational studies and GDG consensus that they should lead to an appropriate change in clinical practice.

d For more information on PSA please see Appendix A.

Clinical evidence (2008)

The literature search found no directly relevant studies comparing immediate and delayed biopsy in men with a raised PSA level. A number of observational studies (Borden *et al*. 2006; Garzotto *et al*. 2005; Krejcarek *et al*. 2007; Nam *et al*. 2006; Thompson *et al*. 2006) reported risk factors for high grade prostate cancer in men referred for sextant prostate biopsy. Odds of high grade cancer were related to age, PSA, DRE result, prior negative biopsy, black ethnicity and prostate volume.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Recommendation	**If the clinical suspicion of prostate cancer is high, because of a high PSA value and evidence of bone metastases (identified by a positive isotope bone scan or sclerotic metastases on plain radiographs), do not offer prostate biopsy for histological confirmation, unless this is required as part of a clinical trial. [2008]**
Qualifying statement	There was strong GDG consensus supported by case series evidence that the above combination allows a sufficiently high probability of an underlying prostate cancer to justify a diagnosis of metastatic prostate cancer without a biopsy.

Clinical evidence (2008)

No directly relevant studies were identified. Evidence from two case series (Vandecandelaere *et al*. 2004; Katagiri *et al*. 1999) suggested the prevalence of prostate cancer in men presenting with bone metastases and unknown primary tumour was around 30%. Case series (Wymenga *et al*. 2001; Gleave *et al*. 1996; O'Sullivan *et al*. 2003; Lin *et al*. 1999; Oesterling 1993) provide evidence about PSA concentration and bone scan results in men with histologically confirmed (but untreated) prostate cancer. These studies allow estimates of the sensitivity of various PSA cut-offs for the detection of prostate cancer in men with bone metastases. A systematic review (Eichler *et al*. 2006) identified 36 studies with data about adverse effects associated with prostate biopsy. The most common were minor bleeding, voiding difficulties and minor infection.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

3.2 Histological diagnosis

3.2.1 Initial biopsy

The diagnosis of prostate cancer is usually confirmed with ultrasound-guided prostate biopsy. Some men will have a diagnosis made on the tissue obtained at TURP.

The PCRMP has recommended a multiple core sampling technique involving at least ten cores covering all parts of the gland and guided by transrectal ultrasound.

Recommendations	**Carry out prostate biopsy following the procedure recommended by the Prostate Cancer Risk Management Programme in Undertaking a transrectal ultrasound guided biopsy of the prostate. [2008]**
Qualifying statement	These recommendations, made in the absence of reliable research evidence, are based on GDG consensus.

3.212 Pre-biopsy imaging

Men with suspected prostate cancer typically receive a trans-rectal ultrasound (TRUS) guided biopsy of the prostate as the initial diagnosis method. However, while TRUS is excellent at showing the prostate and its zonal anatomy, it cannot highlight small foci of tumour. In particular, TRUS is thought to be particularly poor at detecting anterior, apical and central lesions. Therefore TRUS guided biopsies are somewhat limited with biopsies guided to zones within the gland but generally not to suspicious lesions.

Multi-parametric MR imaging consists of a combination of anatomic (T2 weighted) imaging (T2WI) and functional MRI techniques such as dynamic contrast enhanced (DCE) MR, diffusion weighted (DWI) MR and magnetic spectroscopy (MRS). Within a multi-parametric MR imaging examination, the relative value of its component techniques differ. T2WI MR imaging mainly assesses anatomy, DWI and MRSI may add specificity for prostate cancer detection, while DCE-MRI may increase the sensitivity in lesion detection.

Clinical question: Does multiparametric/functional MRI before TRUS biopsy increase diagnostic yield of initial biopsy in men with suspected prostate cancer

Update 2014

Clinical evidence (see also full evidence review) (2014)

Study quality and results

Low quality evidence about diagnostic yield came from four studies (see Tables 10 and 11). The men in these studies received both anatomic and functional magnetic resonance imaging (MRI) before their initial trans-rectal ultrasound (TRUS) guided biopsy for suspected prostate cancer.

All of the studies used cognitive targeting, where review of lesions seen on a pre-biopsy MRI was used to select appropriate targets for TRUS biopsy. One of the studies (Delongchamps *et al*. 2013) also examined MRI-TRUS image registration for navigation during prostate biopsy. Three of the studies (Haffner *et al*. 2011; Belas *et al*. 2012; Delongchamps *et al*. 2013) considered the clinical significance of the detected cancers.

The studies were not typical diagnostic accuracy studies: as there was no reference standard test it was only possible to compare the prostate cancer detection rates of the various strategies. Men without lesions on MRI received fewer biopsy cores than those with lesions seen on MRI – which could confound estimates of the effectiveness of MRI targeted plus systematic biopsy. Systematic biopsies were not done blind to the results of the MRI and this could increase the detection rate of systematic biopsy. The delay between the pre-biopsy MRI and the prostate biopsy was not reported in the included studies.

Evidence about harms associated with TRUS biopsy came from a systemic review by Eichler *et al*. (2006; see Table 12).

Evidence statements

Diagnostic yield of combined MRI targeted and systematic biopsy versus systematic biopsy

Evidence from observational studies indicates that cognitively targeting TRUS biopsies using pre-biopsy multi parametric MR (mp-MRI) increase the prostate cancer detection rate by around 2%. This suggests that for every 100 men using a mp-MRI targeted biopsy in addition to systematic TRUS biopsy instead of systematic TRUS biopsy alone we could expect to detect an additional two cases of prostate cancer. These studies suggest that the extra cases identified by mp-MRI targeted biopsies are not micro focal prostate cancers.

Evidence from one study (Delongchamps *et al*. 2013) suggests that using MRI-TRUS image registration during prostate biopsy has a higher prostate cancer detection rate than cognitively guided MRI targeted biopsy. TRUS biopsy navigation using rigid MRI and ultrasound registration increased prostate cancer detection rate by 14% when compared to systematic TRUS biopsy alone. TRUS biopsy navigation using elastic MRI and ultrasound registration increased prostate cancer detection rate by 20%. Again the majority of the extra cases detected using MRI targeting were not micro focal prostate cancer.

Update 2014

Morbidity due to biopsy

Evidence from a systematic review (Eichler *et al*. 2006) suggests TRUS guided biopsy has serious adverse event rates of 0 to 2% for serious infection (for example bacteraemia, urosepsis or abscess) and 0 to 1% for serious bleeding. Minor adverse event rates were: infection in 0%-7%, haematuria in 1%-95%, haematospermia in 2%-95% and rectal bleeding in 2%-95%.

Table 10: Diagnostic yield of prostate cancer from cognitive from TRUS biopsies targeted using pre-biopsy multi-parametric MRI

				Prostate cancer detection rate per patient			
Study	**MRI sequence**	**Navigational system for biopsy**	**Proportion of men with lesions on MRI**	**MRI-targeted cores**	**Standard systematic cores**	**Combined MRI targeted plus systematic cores**	**Absolute difference (combined – standard)**
Haffner *et al*. (2011)	T2/DCE	US (cognitive)	351/555 (63.2%)	236/555 (42.5%)	290/555 (52.3%)	302/255 (54.4%)	2.1%
Park *et al*. (2011)	T2/DCE/DWI	US (cognitive)	23/44 (52.3%)	9/44 (20.5%)	12/44 (27.3%)	13/44 (29.5%)	2.2%
Belas *et al*. (2012)	T2/DCE/DWI	US (cognitive)	37/71 (52.1%)	24/71 (33.8%)	35/71 (49.3%)	38/71 (53.5%)	4.2%
Delongchamps *et al*. (2012)	T2/DCE/DWI	US (cognitive)	54/127 (42.5%)	40/127 (31.5%)	55/127 (43.3%)	58/127 (45.7%)	2.4%
Delongchamps *et al*. (2012)	T2/DCE/DWI	Rigid MRI-TRUS image registration	78/131 (59.5%)	64/131 (48.9%)	60/131 (45.8%)	78/131 (59.5%)	13.7%
Delongchamps *et al*. (2012)	T2/DCE/DWI	Elastic MRI-TRUS image registration	82/133 (61.6%)	62/133 (46.7%)	44/133 (33.0%)	71/133 (53.4%)	20.4%

Update 2014

Table 11: Diagnostic yield of clinically significant prostate cancer from cognitive targeting of TRUS biopsies using pre-biopsy multi-parametric MRI

					Prostate cancer detection rate per patient			
Study	**MRI sequence**	**Navigational system for biopsy**	**Definition of clinically significant cancer**	**Proportion of men with lesions on MRI**	**MRI-targeted cores**	**Standard systematic cores**	**Combined MRI targeted plus systematic cores**	**Absolute difference (combined – standard)**
Haffner *et al*. (2011)	T2/DCE	US (cognitive)	More than 5mm length of cancer in a core and/or any Gleason >3.	351/555 (63.2%)	236/555 (42.5%)	237/555 (42.7%)	249/555 (44.8%)	2.1%
Belas *et al*. (2012)	T2/DCE/DWI	US (cognitive)	NOT micro focal cancer (single core, < 4mm Gleason 3+3)	37/71 (52.1%)	24/71 (33.8%)	25/71 (35.2%)	28/71 (39.4%)	4.2%
Delongchamps *et al*. (2012)	T2/DCE/DWI	US (cognitive)	NOT micro focal cancer (single core, < 5mm Gleason 3+3)	54/127 (42.5%)	40/127 (31.5%)	43/127 (33.9%)	46/127 (36.2%)	2.3%
Delongchamps *et al*. (2012)	T2/DCE/DWI	Rigid MRI-TRUS image registration	NOT micro focal cancer (single core, < 5mm Gleason 3+3)	78/131 (59.5%)	58/131 (44.3%)	45/131 (34.4%)	60/131 (45.8%)	11.4%
Delongchamps *et al*. (2012)	T2/DCE/DWI	Elastic MRI-TRUS image registration	NOT micro focal cancer (single core, < 5mm Gleason 3+3)	82/133 (61.6%)	58/133 (43.4%)	35/133 (26.3%)	60/133 (45.1%)	18.8%

Update 2014

Table 12: Adverse events according to number of cores in TRUS biopsy, from Eichler *et al*. (2006)

		Major adverse events %		Minor adverse events %				Other adverse events %	
Number of cores	**No. of studies**	**Infection**	**Bleeding**	**Infection**	**Haematuria**	**Haemospermia**	**Rectal bleeding**	**Voiding difficulties**	**Pain (discomfort or mild-severe)**
6 Cores	6	0	0	0.0–6.0	17.6–58.0	65.0–79.0	2.0–18	0	32
8 Cores	4	NR	0.6	1.1–6.9	5.0–71.4	2.0–27.8	2.0–33.8	0.5–1.9	NR
10 Cores	8	0.9	0.3–0.6	2.3–2.6	1.6–72	75	29	0.8–2.6	27.9–33
12/13 Cores	13	0.0–0.7	0	0.0–5.2	0.8–80.0	6.2–82.0	0.7–23.0	0.0–7.2	6.0–33.3
14 Cores	4	1.8	NR	0.0–3.9	5.3–95.0	24.7–95.0	7.9–95.0	4.9–5.4	6.9–64.8†
18 Cores or greater	5	0	0.0–0.3	NR	84	60	45	2	NR

Abbreviations: NR = not reported.

Cost-effectiveness evidence (see also full evidence review) (2014)

Background and aims

Multiparametric magnetic resonance imaging (mpMRI) techniques have been used in the diagnosis of prostate cancer. These techniques are known to improve the accuracy of biopsies but they are substantially more costly and so may not be cost-effective. This economic evaluation aimed to assess the cost-effectiveness of mpMRI before TRUS guided prostate biopsy in men with suspected prostate cancer. The analysis considered the perspective of the National Health Service (NHS).

Methods

Economic evidence review

A systematic literature review was performed to assess the current economic literature in this area. The review identified 827 possibly relevant economic papers relating to prostate cancer. Of these, 824 papers were excluded based on the titles and abstracts and thus three full papers relating to the topic at hand were obtained for appraisal.Two of these papers were excluded as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore only one paper, Stadlbauer *et al* 2011, was included in the review of published economic evidence for this topic.

It should be noted that the paper was written in a non-English language (German) and as such would not typically be included in the evidence review. However, given the paucity of other evidence available in this area, an exception was made.

The study estimated the cost-effectiveness of MRI in the diagnosis of prostate cancer prior to the first biopsy and included an analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis. The use of MRI prior to biopsy was found was found to be more effective and more costly than biopsy alone and provided one additional QALY at a cost of €41,331. The authors concluded that it was difficult to make a clear recommendation for or against the use of MRI.

However, the study was deemed to be only partially applicable to our decision problem. This is primarily because the study considered a German health care perspective and, as such, its applicability to the UK health care setting may be limited. Furthermore, potentially serious limitations were identified with the study. Perhaps most notably, a probabilistic sensitivity analysis (PSA) was not conducted.

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. This evaluation was based on an existing discrete event simulation (DES) model developed by the London School of Hygiene and Tropical Medicine (LSHTM). The LSHTM designed the model as a way of assessing the feasibility of using full treatment pathway models in guideline development. As such, the model fully covers the period that is relevant to the decision problem. It starts with men entering secondary care with an elevated PSA and follows them through the various diagnostic, treatment and management strategies that they may need until they die.

The underlying disease progression rate in the model was informed by the watchful waiting arm of a study of 695 men with localised prostate cancer (Bill Axelson *et al*. 2011). Patients receiving radical treatment are assumed to have a reduced rate of progression and follow the local progression rates observed in the radical prostatectomy arm of Bill Axelson *et al*. 2011.

Update 2014

The model was adapted to allow for different diagnostic interventions to be applied to the patients entering with elevated PSA (i.e. patients with and without prostate cancer), with the results of the clinical evidence review used to inform the diagnostic accuracy rates in the model.

The results of the evidence review showed that the accuracy improvement associated with adding mpMRI targeted cores to systematic cores is dependent upon the targeting technique that is used. Cognitively targeting TRUS biopsies using a pre-biopsy mpMRI was shown to increase the cancer detection rate by around 2% in comparison to systematic biopsy (Moore *et al*. 2013, Haffner *et al*. 2011, Park *et al*. 2011, Belas *et al*. 2012 and Delongchamps *et al*. 2013). Whereas, TRUS biopsy navigation using mpMRI and ultrasound registration, in comparison to systematic biopsy alone, increased prostate cancer detection by 14% and 20% when using rigid and elastic registration respectively (Delongchamps *et al*. 2013).

Thus, in our analysis we separately considered strategies using cognitive targeting and fusion targeting. In each case, it was assumed that the mpMRI guided cores would be taken in addition to the systematic cores.

Note that the results of the clinical evidence review also suggested that a strategy of only biopsying men with positive mpMRI results (i.e. targeted biopsies only) may be beneficial by reducing the number of unnecessary biopsies undertaken. However, the GDG had reservations about the evidence base in this area and were uncomfortable with a targeted biopsy strategy because of the possibility of missing potentially significant cancers. Therefore this strategy was not incorporated in the base case analysis but is explored further in one of the sensitivity analyses.

The model estimates total life years, quality adjusted life years (QALYs) and costs for the simulated patient. The costs reflect the monitoring, management or treatment strategies that the patient may receive, including drug costs, treatment costs or any other resource use that may be required (e.g. GP visit). The majority of costs were sourced from NHS reference costs 2011/12 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dose and unit cost information from the British National Formulary (BNF), resource use and cost information from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

Update 2014

In terms of benefits, each health stage of disease has an associated quality of life (QoL) value. This reflects the model's measurement of benefits in terms of QALYs, whereby the quantity and quality of life can be expressed simultaneously. All utility estimates were sourced from published studies, with an effort made to best reflect the appropriate patient population.

The overall costs and benefits for each treatment are then estimated based on the total length of time individuals spend in each health state over the modelled time horizon. Costs and benefits were discounted at 3.5% per year as recommended by NICE.

Results

The base case cost-effectiveness results of the model are presented in table 13. It can be seen that the effectiveness and cost-effectiveness of using mpMRI before a systematic biopsy depends upon the targeting system that is used. The cognitive targeting approach was found to be less effective than systematic TRUS biopsy (8.79 vs 8.81 QALYs) and less costly (£10,064 vs £9,897). This results in an estimated ICER of £7,425 per QALY. Given that both the incremental costs and benefits are negative; this value needs to be interpreted with caution. It implies that, for every QALY lost by using the cognitive targeting strategy, £7,425 is saved. For the strategy to be considered cost-effective, this saving needs to exceed the WTP threshold. Thus, at the commonly accepted WTP threshold of £20,000 per QALY, this strategy would not be considered cost-effective.

The results for the fusion targeting approach were very different as it was found to be more effective (0.009 QALYs) and more costly (£326) than the systematic TRUS biopsy strategy. This results in an estimated ICER of £35,341 per QALY i.e. a systematic + fusion mpMRI biopsy strategy provides one additional QALY at a cost of £35,341, in comparison to systematic TRUS biopsy. Therefore, at a willingness to pay threshold (WTP) of £20,000 per QALY, this strategy would not be considered cost-effective.

Table 13: Base case total expected costs, QALYs and ICER per patient

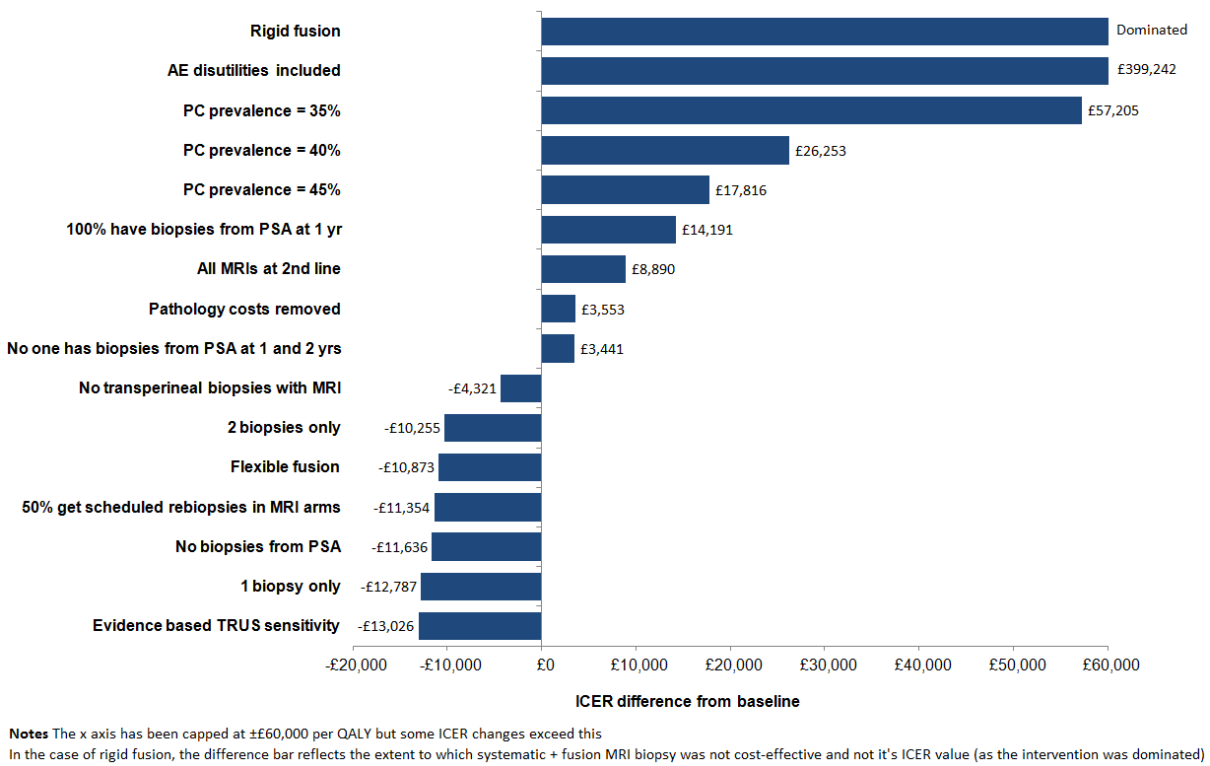
Treatment options	Total QALYs	Incremental QALYs	Total costs	Incremental costs	ICER
Systematic TRUS biopsy	8.813	-	£10,064	-	-
Systematic + cognitive mpMRI biopsy	8.791	-0.022	£9,897	-£167	£7,423
Systematic + fusion mpMRI biopsy	8.822	0.009	£10,390	£326	£35,341

Sensitivity analysis

One-way sensitivity analysis was conducted to estimate the influence of changing some key assumptions; the results are shown in the figure below. Note that the analysis focuses on the comparison of systematic TRUS biopsy and systematic + fusion mpMRI biopsy as the systematic + cognitive mpMRI biopsy strategy remained the least preferred strategy in all modelled analyses. The x axis shows the difference in ICER value compared to the base case ICER with the vertical line representing the base case ICER result. Values to the left of the vertical line show that the ICER is lower than in the base case (i.e. more cost-effective) and values to the right of the vertical line show that the ICER is higher than in the base case (i.e. less cost-effective).

Update 2014

Figure 55: Results of one-way sensitivity analysis



Notes The x axis has been capped at ±£60,000 per QALY but some ICER changes exceed this
In the case of rigid fusion, the difference bar reflects the extent to which systematic + fusion MRI biopsy was not cost-effective and not it's ICER value (as the intervention was dominated)

The results show that the model is sensitive to numerous input parameters within the model with systematic TRUS + fusion mpMRI biopsy found to be nearly cost-effective with an ICER of £22,316 per QALY to be being dominated (i.e. less effective and more costly than systematic TRUS biopsy). In particular, the underlying prostate cancer prevalence rate, the sensitivity of TRUS biopsy, the type of fusion mpMRI that is used (flexible or rigid) and the inclusion of adverse event related disutilities. However, notably, the ICER value did not fall below a WTP threshold of £20,000 per QALY in any of the modelled scenarios.

Probabilistic sensitivity analysis showed that, at a threshold of £20,000 per QALY, systematic TRUS biopsy was likely to be the preferred strategy with a 94% probability of being considered cost-effective. Systematic + fusion MRI biopsy had only a 6% probability of being considered cost-effective at this threshold.

Conclusion

In conclusion, the economic analysis suggests that the cost-effectiveness of biopsying additional cores identified using mpMRI is dependent upon the targeting strategy that is employed. Cognitive targeting was not found to be cost-effective in any of the modelled analyses whilst the cost-effectiveness of fusion targeting was substantially better. However, the ICER associated with fusion targeting was above £30,000 per QALY and so would not be considered cost-effective at the WTP thresholds commonly accepted by NICE.

However, it should be acknowledged that the analysis does suggest that there could be substantial benefits associated with the use of MRI before diagnosis. This is particularly true in the analysis where it was assumed that biopsies would not be performed in patients with a negative mpMRI. In this strategy costly and detrimental (in QoL terms) potentially unnecessary biopsies could be avoided. However, further evidence will be required to convince clinicians that mpMRI does not miss a substantial amount of significant cancers.

Note that the conclusions must also be tempered by the limitations of the analysis. Most notably, the limitations of the clinical evidence upon which the analysis is based and the considerable uncertainty that necessitated that strong assumptions be made in some areas. There appears to be a need for better evidence in this area to be able to better assess the cost-effectiveness of this potentially useful and practice changing intervention.

Update 2014

Recommendations	No recommendation made
Relative value placed on the outcomes considered	The GDG considered diagnostic yield to be the most important outcome when assessing the utility of performing MRI before TRUS biopsy. However, the GDG were uncertain whether this would lead to an increase in the rate of detection of clinically significant cancers. No evidence was found for the outcomes of health-related quality of life or diagnostic related mortality. Because of the uncertainty about the effect of performing an MRI before biopsy on morbidity, the GDG did not consider the outcome of diagnostic related morbidity.
Quality of the evidence	The evidence base for the four included studies was assessed as being of low quality for the following reasons. The studies did not include an exhaustive reference standard test for prostate cancer so it was only possible to compare their prostate cancer detection. Men without lesions on MRI received fewer biopsy cores than those with lesions seen on MRI – which may underestimate the incidence of cancer and could confound estimates of the effectiveness of MRI targeted plus systematic biopsy. Systematic biopsies were not done blind to the results of the MRI and this could increase the detection rate of systematic biopsy. The delay between the pre-biopsy MRI and the prostate biopsy was not reported in the

	included studies.
Trade-off between clinical benefits and harms	The GDG noted the wide variation in clinical protocols involving mpMRI and subsequent biopsy. Some centres use cognitive-targeting of biopsies whereas others use image registration. In addition, there is variation in the type of biopsy used. The GDG also acknowledged that clinical practice in this area is rapidly evolving. The GDG were therefore uncertain about the benefits and harms associated with performing an MRI and biopsy strategy. The GDG were also uncertain what effect being diagnosed at an earlier stage would have on subsequent treatment and overall survival. The GDG noted that the body of evidence predominantly covers post biopsy and there is a lack of evidence in the use of MRI pre-biopsy and in long term follow up. Although not imaging prior to biopsy may appear to be paradoxical when men are imaged further down the pathway, the GDG felt current evidence does not give sufficient support to recommend this.
Trade-off between net health benefits and resource use	The GDG noted that the results of the economic model showed that the cost-effectiveness of biopsying additional cores identified using mpMRI in addition to a systematic biopsy is dependent upon the targeting strategy that is employed. Cognitive targeting was not found to be cost-effective in any of the modelled analyses whilst the cost-effectiveness of fusion targeting was substantially better. However, the ICER associated with fusion targeting was £35,341 per QALY and so would not be considered cost-effective at a willingness to pay threshold of £20,000 per QALY. The results were found to be sensitive to changes in many of the input parameters and assumptions with wide ranging ICER results, reflecting the uncertainty in this area. However, the conclusions remained the same in all modelled scenarios with cognitive targeting found to be the least preferred option and fusion targeting found to be more effective but not cost-effective as the ICER remained above a willingness to pay threshold of £20,000 per QALY. Despite the intervention not being cost-effective, the GDG acknowledged that there could be substantial benefits associated with the use of MRI before diagnosis. However, it was thought that the current evidence base is not sufficient to be able to fully assess the potential harms, benefits and costs of using MRI before biopsy. This is particularly true when considering a strategy where biopsies would not be performed in patients with a negative mpMRI. Further high quality evidence expected to be generated by the PROMIS trial could address these uncertainties. The combination of uncertainty over clinical protocols, the rapidly evolving clinical practice and the lack of robust cost-effectiveness results led the GDG to make no recommendations for clinical practice.
Other	The GDG noted that the ongoing PROMIS trial is investigating the optimal MRI and biopsy strategy, and so agreed not to make a recommendation for further research.

Update 2014

3.2.13 Management of men with a negative inital biopsy

A single negative prostate biopsy does not definitively exclude the presence of cancer. Men who have had one negative biopsy may still have prostate cancer. Factors such as raised PSA, abnormal DRE, PSA kinetics, pathological features on biopsy and biomarkers (for example PCA3) may indicate undetected prostate cancer.

Clinical question: In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy.

Clinical evidence (see also full evidence review) (2014)

Study quality and results

Twenty-five studies assessed age as a predictive factor for prostate cancer at re-biopsy, 27 studies assessed PSA level at initial biopsy, 18 assessed free-to-total PSA at initial biopsy, nine assessed PSA density, ten assessed PSA velocity, 18 assessed abnormal DRE, 12 studies reported on PIN or HGPIN as a predictive factor, six studies assessed ASAP and one AGSC, 12 assessed biomarker PCA3, two assessed family history, and one assessed ethnicity. The evidence was of low to moderate quality, with the prognostic factor of interest influencing whether patient underwent repeat biopsy in many of the studies and many of the models did not include important confounding factors such as age, free-to-total PSA, or prostate volume.

Evidence statements

Age

Six (33%) of 18 very low quality studies found age to be a significant predictor in a univariate model (where reported the odds ratio (OR) ranged 1.04-1.08). Three (21%) of 14 studies found age to be a significant predictor in a multivariate model once other potentially confounding variables had been taken into account (OR 1.01-1.09). One very low quality study also found those aged > 64 and > 69 years to be significantly more likely to have prostate cancer at re-biopsy in univariate and multivariate models respectively (OR 3.24) (Singh *et al*. 2004). While one moderate quality study found no significant difference between those ages ≤ 60 and > 60 years in univariate or multivariate models (Campos-Fernandez *et al*.2009).

PSA level at first biopsy

Six (33%) of 18 studies found PSA level to be a significant predictor in a univariate model (where reported OR 1.01-1.04). Three (21%) of 14 multivariate models also found PSA level to be a significant predictor (where reported OR 1.02-1.04). One very low quality study also found those with PSA 4-10 ng/ml compared to PSA < 4 ng/ml were not significantly more likely to have prostate cancer at re-biopsy in univariate or multivariate models (Bollito *et al*. 2012). While Campos-Fernandez (2009) found that PSA > 4 ng/ml was a significant predictor in a univariate model but PSA > 10 ng/ml was not a predictor in either univariate or multivariate models. Sensitivity and specificity were not consistent for similar PSA levels between six very low quality studies and showed no clear trend with increasing cut-off level; demonstrating low overall diagnostic accuracy.

Free-to-total PSA at first biopsy

Seven (50%) of 14 studies found PSA level to be a significant predictor in a univariate model (where reported OR 0.91-0.97). Four (44%) of nine multivariate models also found ftPSA to be a significant predictor (where reported OR 0.87-1.40). Two very low quality studies also both found ftPSA > 2.0 to be significant in univariate models but not multivariate models. One moderate quality study also found a ftPSA > 0.15 to be a significant predictor in a univariate model but not in a multivariate model (Campos-Fernandez *et al*. 2009). Sensitivity and specificity were not consistent for similar PSA levels between five very low quality studies

Update 2014

and showed no clear trend with increasing cut-off level; demonstrating low overall diagnostic accuracy.

PSA density at first biopsy

Five (71%) of seven low quality studies found PSAd to be a significant predictor in a univariate model, though none reported an OR, and three (75%) of four low quality multivariate models found PSAd to be a significant predictor (where reported OR 1.01-24.7). One low quality study also found those with PSAd > 0.15 ng/ml/ml to be significantly more likely to have prostate cancer at re-biopsy in a multivariate models accounting for five other variables (OR 2.3 95% CI 1.4–4.0) (Wu *et al*. 2012). Two studies treated PSAd as a categorical variable; both Campos-Fernandez *et al*. (2009) and Wu *et al*. (2012) provided low quality evidence that those with PSAd > 0.15 ng/ml/ml were significantly more likely to have prostate cancer at re-biopsy in a multivariate models (OR 2.3 in both studies).

PSA velocity at first biopsy

Four (50%) of eight studies found PSAv to be a significant predictor in a univariate model, as did all three (100%) of the multivariate models (where reported OR 1.34-1.58). Three low quality studies treated PSA velocity at initial biopsy as a categorical variable; both Campos-Fernandez *et al*. (2009) and Naya *et al*. (2004) did not find a PSAv ≥ 0.75 ng/ml/year to be a significant predictor in either univariate or multivariate models. Singh *et al*. (2004) did not find a PSAv > 0.93 ngml/year to be a significant predictor in a univariate model. Two very low quality studies treated PSAv at initial biopsy as a categorical variable and found it was not a significant predictor in uni- or multivariate models (cut-off levels of PSAv ≥ 0.75 and > 0.93 ng/ml/year). Sensitivity and specificity showed no clear trend with increasing cut-off level and demonstrated low overall diagnostic accuracy in four very low quality studies.

Abnormal DRE at first biopsy

Four (33%) of 12 studies found it to be a significant predictor in a univariate model (where reported OR 2.65-2.80), and five (38%) of 13 multivariate models found it to be a significant predictor (where reported OR 2.63-4.61). Eight very low quality studies reported low overall diagnostic accuracy for abnormal DRE at initial biopsy, with most reporting low sensitivity but high specificity.

Pathological features at first biopsy

One (50%) study found the presence of prostatic intraepithelial neoplasia (PIN) to be a significant predictor and two (23%) of seven studies found high grade PIN (HGPIN) to be a significant predictor in a univariate model (where reported OR 5.07). Four (50%) of eight multivariate models found HGPIN to be a significant predictor (where reported OR 1.38-3.2). Five very low quality studies reported low overall diagnostic accuracy for the presence of HGPIN at initial biopsy.

Two (50%) of four studies found atypical small acinar proliferation (ASAP) to be a significant predictor in a univariate model (OR 2.79-3.12). All four (100%) of the multivariate models found ASAP to be a significant predictor (OR 2.97-3.65). Two low quality studies reported diagnostic accuracy for the presence of ASAP at initial biopsy, both suggesting low sensitivity but high specificity. One study also found atypical glands suspicious for carcinoma (AGSC) at initial biopsy to be a predictive factor of prostate cancer at re-biopsy in both a univariate and two multivariate models (where reported OR 20.71).

PCA3 score at first biopsy

All of three univariate models (100%) and the only (100%) multivariate model found PCA3 to be a significant predictor (where reported OR 1.02). Three studies (100%) also found a

Update 2014

significant difference in malignancy rates at re-biopsy in univariate models for various cut-off levels, ranging from 15 to 70. Two of the studies also assessed PCA3 score in multivariate models and found it to remain significant once 2-6 other variables had been taken into account, for cut-off scores of 30, 39 and 50. Sensitivity and specificity were not consistent in 12 very low quality studies and showed no clear trend with increasing cut-off level; demonstrating low overall diagnostic accuracy.

Family history of prostate cancer, ethnicity and clinical stage

Both of two studies (100%) found family history to be a significant predictor in multivariate models (where reported OR 3.1). Another study (Lee *et al*. 2011) found no significant difference between those of Caucasian ethnic origin and those not in a multivariate model. One moderate quality study found no significant difference between those with stage T1 and those with T2 in either a univariate or a multivariate model (Campos-Fernandez 2009).

Update 2014

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. No further economic modelling was undertaken because identifying prognostic factors that determine the need for further investigation was a clinical issue and therefore not appropriate for modelling.

1

Recommendations	**The results of all prostate biopsies should be reviewed by a urological cancer MDT. If a biopsy is negative, rebiopsy should be offered only after an MDT review of the man's risk factors. [2008, amended 2014]** **If the first biopsy is negative, advise the man that:** • **there is still a risk that prostate cancer is present and** • **the risk is slightly higher if any of the following risk factors are present:** o **prostate cancer antigen 3 (PCA3) is above 35** o **the biopsy showed high-grade prostatic intra-epithelial neoplasia** o **the biopsy showed atypical small acinar proliferation (ASAP).** **[new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcome of diagnostic accuracy to be the most important as it would show which prognostic factors were significant predictors of cancer.
Quality of the evidence	There was very low quality evidence for the prognostic factors of age, PSA level, free-to-total PSA, PSA velocity, abnormal DRE, PIN, high-grade PIN, ASAP, PCA3 score, family history and ethnicity. The evidence for PSA density was low quality. The GDG noted the following limitations with the evidence: • the duration between biopsies was unclear in many studies and was sometimes more than 1 year, meaning a new malignancy could have developed in this time. • Several studies excluded important potential confounding factors from their statistical models. • The way tests were performed and the way results were interpreted was poorly reported. • The reference standard depended on the index test result for several studies. The GDG took account of these limitations when making recommendations.
Trade-off between clinical benefits and harms	Based on the evidence, the GDG noted that there were no prognostic factors that reliably showed there was no risk of prostate cancer following a negative initial biopsy. They agreed that this information should be shared with men to prevent any false reassurance that the negative biopsy meant no cancer was present. The GDG acknowledged that because prognostic factors could not be used to rule out prostate cancer, further investigation would be needed. Men could potentially experience anxiety while a definitive diagnosis was obtained and some men would have unnecessary investigations and the adverse effects associated with them. However the GDG considered that it was important to share this information with men so that they could make informed decisions on their own management. Based on the evidence, the GDG noted that the presence of high-grade PIN, atypical small acinar proliferation and an elevated PCA3 score were all associated with a statistically significant increased risk of prostate cancer in subsequent biopsies. By discussing these factors with men found to have them (following a negative initial biopsy), it would be possible to highlight the potential increased risk associated with these factors. However it would not be possible to quantify this risk, which could cause additional anxiety. The GDG agreed that the potential harm was outweighed by the benefit of providing a man with more information. The

Update 2014

	GDG also agreed that because PCA3 score is not measured as part of current practice, guidance was needed on what constituted an elevated score.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG agreed that making these recommendations would not have any direct cost implications as discussion of these issues is likely to be already happening in clinical practice. However the GDG acknowledged that as a result of making these recommendations, additional men may decide to have a PCA3 test to inform the discussion. This would be an additional cost but it was not possible to quantify what this would be.

The optimal course of action in men who are still suspected of having prostate cancer following a negative initial TRUS biopsy is not well defined. The following may be considered review of initial biopsy, repeat TRUS biopsy, multiparametric MRI, extended/saturation TRUS biopsy, 3D ultrasound plus biopsy, template biopsy, contrast enhanced ultrasound plus biopsy, and/or elastography plus biopsy.

Clinical question: In men with suspected prostate cancer whose initial TRUS biopsy is negative what should be the next investigation(s).

Clinical evidence (see also full evidence review) (2014)

Study quality and results

Update 2014

Evidence on MRI, MRS and repeat TRUS came from a systematic review (Mowatt *et al*. 2013) including 51 studies and three more recent studies. Thirty-five case-series studies and four cohort studies reported the diagnostic yield of extended/saturation biopsy, seven studies reported the results of repeat TRUS, and five studies reported on the use of contrast-enhanced ultrasound. One small study compared elastosonography rebiopsy and contrast enhanced ultrasound rebiopsy (Morelli *et al*. 2009). Another study compared initial diagnosis by consultant pathologists with a reference standard diagnosis by consultant pathologists with a special interest in uropathology (Oxley and Sen 2011). Risk of bias in patient selection and the index test was assessed as low in the majority of studies. Most studies used a representative sample of patients, who were referred to repeat biopsy due to persistently elevated PSA levels and/or abnormal DRE despite previous negative biopsies.

Evidence statements

Multi-parametric MRI targeted biopsy

Evidence suggests that a strategy in which only men with visible pathology on multi-parametric MRI were re-biopsied (using TRUS guided biopsy with both MRI targeted and systematic cores) would mean fewer men re-biopsied compared to a routine systematic re-biopsy strategy. The sensitivity for prostate cancer varies from around 79% to 96% depending on the MRI sequences used (see Table 14) - meaning that a proportion of cancers (approximately 4% to 21%) would be missed if such a testing strategy was used. (Mowatt *et al*. 2013).

Nelson *et al* (2013) estimated the relative prostate cancer detection rates of repeat biopsy strategies using meta-regression of 46 studies. The rate of prostate cancer detection was 37.6% using MRI targeted re-biopsy, 36.8% using transperineal saturation biopsy and 30.0% using transrectal saturation biopsy. These differences were not statistically significant following adjustment for the number of previous biopsies.

Mowatt *et al*. (2013) summarised the adverse effects of testing in their systematic review of multi-parametric MRI targeted re-biopsy. Ten studies reported adverse effects all of which appeared to be related to TRUS-guided biopsies rather than MRI procedures. Serious adverse events included prostate haemorrhage (5% in one study), severe vasovagal episodes (1.4% to 1.5%), sepsis or fever (0.4% to 2.3%), acute urinary retention (2.3%), and severe rectal bleeding (0.1% to 0.5%).

Extended/saturation biopsy

Cancer detection rate appears to increase with the number of re-biopsy cores, although there is variability between studies in the reported rates. The pooled proportion of tests positive for cancer is approximately 20% for repeat TRUS biopsy (10 to 12 cores), 20% for TRUS extended biopsy (12-14 cores), 30% for TRUS saturation biopsy (median 24 cores) and 40% for transperineal saturation biopsy (median 29 cores). The pooled proportion of detected cancers considered clinically significant (according to the individual study definitions) was 27% for repeat TRUS 10-12 core biopsy, 60% for TRUS extended biopsy, 57% for TRUS saturation biopsy, and 62% for transperineal saturation biopsy.

Twenty-seven studies reported adverse events due to saturation biopsy (see Table 15). The pooled adverse event rates for transrectal saturation biopsy are 3.8% urinary retention, 5% rectal bleeding, 8.8% haematuria and 3.9% acute prostatitis. The corresponding rates for transperineal saturation biopsy are 6.8% urinary retention, 23.4% haematuria and 0.8% acute prostatitis.

Enhanced ultrasound biopsy

Two small studies reporting on Power Doppler enhanced ultrasound gave a pooled cancer yield of 30% (13/44). In Remzi *et al*. (2004), only one out of the nine cancers detected was found solely from targeted cores.

Two studies reporting on Colour Doppler enhanced ultrasound gave a pooled cancer yield of 20.8% (117/562). Taverna *et al*. (2011) compared Colour Doppler ultrasound with or without microbubble ultrasound contrast agent against TRUS grey-scale 13-core systematic biopsy sampling, finding no differences in cancer detection rates between groups (29% versus 28% versus 31%).

Elastography

Evidence about elastosonography re-biopsy is limited to a single small study published as an abstract only (Morelli *et al*. 2009). In this study all men undergoing elastosonography had areas of increased texture and cancer was detected in 33% (3/9).

Review of initial biopsy

A study of 3,051 prostate biopsies in 2,516 non-screened men (Oxley and Sen 2011) found that 1.2% of biopsies initially classified as benign were changed to cancer on review by a pathologist with special interest in uropathology. Of those biopsies with an initial HGPIN diagnosis, 1.5% were changed to cancer on review and of those biopsies an initial diagnosis of suspicious for malignancy the figure was 4.9%. Of those biopsies with an initial positive result, 0.4% were changed to benign and 0.1% to suspicious on review.

Update 2014

Table 14: Diagnostic accuracy and cancer yield of systematic biopsy, MRI, MRS and TRUS to predict re-biopsy result following an initial negative biopsy (24% prevalence) (Mowatt *et al*. 2013)

Test	Number of studies (participants)	Median prevalence of prostate cancer (range)	Pooled sensitivity % (95% CI)*	Pooled specificity % (95% CI)*	Estimated cancer yield (95% CI)†	Estimated proportion of men re-biopsied (95% CI)†
Systematic extended core TRUS-guided biopsy (14-16 cores)	1 (340)	28%	83 (78 to 88)	1.00	20% (20% to 22%)	100%
MRS	10 (438)	35% (10% to 49%)	92 (86 to 95)	76 (61 to 87)	55% (41% to 70%)	40% (31% to 52%)
DCE-MRI	3 (209)	49% (25% to 54%)	79 (69 to 87)	52 (14 to 88)	34% (20% to 70%)	55% (26% to 86%)
T2-MRI	15 (620)	36% (10% to 54%)	86 (74 to 93)	55 (44 to 66)	38% (29% to 46%)	55% (44% to 65%)
MRS OR T2-MRI	8 (316)	35% (29% to 41%)	96 (90 to 98)	31 (21 to 42)	31% (26% to 35%)	75% (66% to 84%)
DCE-MRI OR T2-MRI	3 (173)	39% (25% to 54%)	88 (80 to 96)	14 (8 to 20)	24% (22% to 27%)	86% (80% to 93%)

**Reference standard differs for extended cores TRUS/Bx and MRI methods. A 24 core TRUS-guided saturation biopsy serves as the reference standard for the extended cores estimate, whereas MRI methods were validated on histopathology of targeted cores and a varying number of additional cores taken under TRUS guidance.*
† Cancer yield is defined as the proportion of men re-biopsied whose results are positive for cancer. The testing strategy assumes that only men with visible pathology on MRI/MRS would be re-biopsied and that both MRI/MRS targeted and 8 ¬-12 systematic cores would be taken.l

Update 2014

Table 15: Reported complications related to repeat biopsies

Complication	Biopsy approach	Number of studies	Total number of patients	Complication rate N (%)
Urinary retention	Transrectal	5	525	20 (3.8%)
	Transperineal	14	1185	80 (6.8%)
Rectal Bleeding	Transrectal	3	421	5 (1.2%)
	Transperineal	0	-	-
Haematuria	Transrectal	5	487	43 (8.8%)
	Transperineal	8	556	130 (23.4%)1
Acute prostatitis	Transrectal	4	438	17 (3.9%)
	Transperineal	1	128	1 (0.78%)

Update 2014

Cost-effectiveness evidence (see also full evidence review) (2014)

A literature review of published economic evidence identified one relevant paper; a comprehensive report conducted as part of the NIHR HTA programme by Mowatt *et al*. 2013. The study included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis. The primary results of the analysis by Mowatt *et al*. 2013 are summarised in the modified Table 16.

Despite the high economic importance of this topic, no further health economic analysis was undertaken. This is because the economic analysis conducted in this study was deemed to be of sufficiently high equality to be used by the GDG when making their recommendations.

Study quality and results

Mowatt *et al*. 2013 was deemed to be directly applicable to the decision problem that we are evaluating since it considers a UK population and does not have any other applicability issues. No serious limitations were identified with Mowatt *et al*. 2013, however there were some issues identified with the clinical evidence base upon which the analysis was based. This was particularly true of the analysis where diffusion weighted MRI was modelled, where assumed values were used for sensitivity and specificity.

Evidence statements

The base case results from Mowatt *et al*. 2013 suggest that the use of T2-MRI to determine and direct biopsies is cost-effective in comparison with systematic TRUS-guided extended cores biopsy (ICER = £10,626 per QALY). This results from its modest additional cost and slightly improved sensitivity over systematic biopsies.

The more sensitive, enhanced MRI/MRS techniques were not found to be cost-effective in the base case analysis (ICER > £30,000 per QALY). However, these techniques were found to be cost-effective in some of the sensitivity analysis, such as the analysis in a high prevalence cohort (prevalence = 50%) or a scenario where MRS was adjusted to only miss low risk cancer.

Owing to a lack of data on its effectiveness, diffusion weighted (DW) MRI was not included in the base case analysis. However, an illustrative analysis on the use of DW-MRI was conducted where it was assumed that DW-MRI had the same sensitivity as MRS (92%) and the same specificity as T2-MRI (55%). Under these assumptions, DW-MRI was found to have an ICER value of £31,061 per QALY or £24,221 per QALY when comparing it against a common baseline (systematic TRUS).

The results of the probabilistic sensitivity analysis (PSA) showed that none of the diagnostic strategies have a high probability of being preferred on the grounds of cost-effectiveness. At a willingness to pay threshold of £20,000 per QALY, T2-MRI had a 33% probability of being cost-effective.

Update 2014

Table 16: Modified GRADE table showing the included evidence (Mowatt *et al*. 2013) comparing subsequent investigation methods following an initial negative biopsy

Study	Population	Comparators	Costs	Effects	Incremental costs	Incremental effects	ICER	Uncertainty	Applicability and limitations
Mowatt *et al*. 2013 (NIHR HTA)	Men with suspected prostate cancer and elevated prostate specific antigen (PSA) but previously negative biopsy.	Systematic TRUS	£3,895	12.48432 QALYs	Reference case			Numerous one-way sensitivity analyses were conducted in areas of interest to the authors. The results showed the results to be highly sensitive to the input parameters and assumptions made. Depending on the scenario modelled, T2-MRI, systematic TRUS or MRS might be the most cost-effective option. Probabilistic sensitivity analysis (PSA) was also conducted. None of the diagnostic strategies were found to have a high probability of being preferred on the grounds of cost-effectiveness. At a willingness to pay threshold of £20,000 per QALY, each intervention had the following probability of being cost-effective†:	Minor limitations
		T2-MRI	£3,902	12.48498 QALYs	£7	0.00066 QALYs	£10,626 per QALY		
		DW-MRI*	£3,943	12.48629 QALYs	£48	0.00197 QALYs	£24,221 per QALY		
		MRS	£3,952	12.48630 QALYs	£57	0.00198 QALYs	£28,502 per QALY		
		DCE-MRI	£3,984	12.48346 QALYs	£1	-0.00086 QALYs	Dominated		
		T2-MRI or MRS	£4,031	12.48714 QALYs	136	0.00282 QALYs	£48,367 per QALY		
		T2-MRI or DCE-MRI	£4,056	12.48538 QALYs	161	0.00106 QALYs	£152,323 per QALY		

Study	Population	Comparators	Costs	Effects	Incremental costs	Incremental effects	ICER	Uncertainty	Applicability and limitations
								Systematic TRUS - 51% T2-MRI - 33% MRS - 15% DCE-MRI - 1% T2-MRI or MRS - 0% T2-MRI or DCE-MRI - 0% Note that as DW-MRI was not considered part of the base case it was not included in the probabilistic sensitivity analysis.	
	Comments: Note that for simplicity ICER results have been presented in comparison to a common baseline (systematic TRUS). To find the most cost-effective diagnostic strategy a dominance rank should ideally be used or the net monetary benefit (NMB) should be calculated.								

** Not included in base case analysis in Mowatt et al. 2013. Figures based on an illustrative analysis in which DW-MRI was incorporated*
† Probabilities stated are estimations based on readings from a CEAC figure presented in Mowatt et al. 2013

1

Recommendations	**Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound 10–12 core biopsy to determine whether another biopsy is needed. [new 2014]** **Do not offer another biopsy if the multiparametric MRI (usingT2- and diffusion-weighted imaging) is negative, unless any of the risk factors listed in the recommendation on page 121 are present. [new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of diagnostic yield, diagnostic process-related morbidity and/or mortality, and health-related quality of life to be the most important in identifying the most effective investigation following an initial negative TRUS biopsy. Diagnostic process-related mortality and health-related quality of life were not reported by the evidence. Data on the additional outcome of false negative rates in histopathology reporting were also included in the evidence review. The GDG decided not to use these data when making recommendations because the error rate was very low (i.e. not clinically significant) and the GDG agreed this issue would be better addressed through quality assurance mechanisms within pathology. The GDG also agreed that the data on sensitivity and specificity were not helpful because the true negative and true positive rates were unknown.
Quality of the evidence	There was moderate quality clinical and economic evidence for multiparametric MRI and extended/saturation biopsy (both transrectal and transperineal). The GDG noted that the evidence did not report sensitivity or specificity values for diffusion weighted (DW) MRI and instead assumed the same sensitivity as MRS and specificity as T2 MRI. The GDG agreed that these were reasonable assumptions. There was very low quality clinical evidence for elastography and 3D ultrasound. The GDG noted that this evidence comprised a limited number of studies on small numbers of patients. They therefore agreed not to consider this evidence.
Trade-off between clinical benefits and harms	The GDG noted, based on the evidence, that MRI had a similar diagnostic yield to saturation biopsy but less morbidity as it enabled many men to avoid re-biopsy. The GDG applied strong weight to preventing unnecessary biopsies because of the consequent morbidity and additional resource utilisation. The GDG acknowledged that a man with risk factors whose multiparametric MRI was negative should not necessarily have rebiopsy but equally should not be discharged back to primary care. The man should be monitored in secondary care and rebiopsied and reimaged based on PSA kinetics or patient choice.
Trade-off between net health benefits and resource use	The GDG noted that a published economic evaluation had shown diffusion weighted MRI compared to T2 MRI had an ICER of £31,061/QALY, however this was based on standard economic methodology whereby DW MRI was compared against the next most effective intervention (T2 MRI). The GDG agreed that T2 MRI alone was not an appropriate intervention in this population because they were not confident in its negative predictive value. Thus the comparison of DW MRI against systematic TRUS (common baseline) was deemed more appropriate. The published economic evaluation showed that this had an ICER of £24,221/QALY. The GDG noted that the health economic evaluation depended on the assumption that no biopsy would be performed after a negative multiparametric MRI (including diffusion weighted) in men who had already

Update 2014

	had a negative standard 10-12 core TRUS biopsy. This results in a reduction in the number of unnecessary biopsies and partially offsets the cost of the MRI scan.

Update 2014

3.3 Staging classification for prostate cancer

The TNM classification (see Appendix C) is used to stage prostate cancer. It describes the extent of the primary tumour (T stage), the absence or presence of spread to nearby lymph nodes (N stage) and the absence or presence of distant spread, or metastasis (M stage).

The clinical stage is determined from information that is available without surgery. The pathologic stage is based on the surgical removal and histological examination of the entire prostate gland, the seminal vesicles and surrounding structures and, if relevant, pelvic lymph nodes.

The management of prostate cancer will depend on the TNM stage of the disease as well as both biochemical information (e.g. PSA) and pathological information (e.g. Gleason score), which have prognostic value. The optimum treatment for a man with prostate cancer requires an assessment of the risk of metastatic spread as well as the risk of local recurrence. For this, the results of imaging can be assessed in the light of information from clinical nomograms (see section 3.4 for information on nomograms).

3.3.1 Imaging at the time of diagnosis for prostate cancer

Men newly diagnosed with prostate cancer can initially be stratified into those for whom radical treatment is a possibility and those for whom it is not appropriate. The decision about treatment intent will be based on the man's life expectancy, his values, and the anticipated clinical course of the prostate cancer (for more information see Chapter 4).

Recommendations	**Determine the provisional treatment intent (radical or non-radical) before decisions on imaging are made. [2008]** **Do not routinely offer imaging to men who are not candidates for radical treatment. [2008]**
Qualifying statement	There was GDG consensus, in the absence of any research evidence, that this will reduce the amount of inappropriate investigation. The cost effectiveness of routine magnetic resonance imaging MRI could not be concluded (see health economic evaluation under 3.3.2).

Both the clinical presentation and the treatment intent influence the decision about when and how to image the individual. The risk of recurrence of prostate cancer after definitive local treatment is the basis for the stratification of men with localised prostate cancer into risk groups: low, intermediate and high (see Chapter 4 for information on risk groups and Table 17). The recommendations for imaging of localised disease are similarly based on these prognostic groups.

Table 17: Risk groups for localised prostate cancer

Level of risk	PSA		Gleason score		Clinical stage
Low risk	< 10 ng/ml	and	≤ 6	and	T1–T2a
Intermediate risk	10–20 ng/ml	or	7	or	T2b
High risk[e]	> 20 ng/ml	or	8–10	or	≥T2c

Update 2014

[e] High-risk localised prostate cancer is also included in the definition of locally advanced prostate cancer

Imaging may inform the choice between different radical treatments (for example by determining whether the cancer has extended beyond the prostatic capsule). It also assists in the identification of metastatic disease thereby leading to more appropriate treatment options.

3.3.2 Imaging for T-staging and N-staging

The T-stage involves the assessment of the local extent of the primary tumour in the prostate and its relationship to surrounding structures. Using imaging to distinguish between T1 and T2 cancers does not usually affect treatment. But if radical treatment is being considered, it is important to decide whether a tumour is T2 (confined within the prostate) or T3/T4 (spread outside the prostate).

Magnetic resonance imaging (MRI) is now the commonly used imaging technique for T-staging men with prostate cancer. Many of the original publications used now-outdated MRI technology, and the accuracy reported for MRI is improving.

After transrectal prostate biopsy, intra-prostatic haematoma can affect image interpretation for at least four weeks.

It is important to know the nodal status of men with localised disease, as the spread of cancer to the pelvic lymph nodes will affect the choice of treatment. Partin's Tables (Partin *et al*. 2001) are the most commonly used clinical nomograms for determining the risk of nodal spread (see section 3.4 for information on nomograms).

Currently, imaging is of some value for N-staging because computed tomography (CT) and conventional MRI rely on size criteria to assess the likelihood of metastatic spread to the lymph nodes. CT cannot characterise the internal architecture of an enlarged node and MRI (T21 and DWI) is only able to provide partial information. Newer MRI contrast agents such as superparamagnetic iron oxide (SPIO) may improve the overall specificity of MRI for evaluating lymph nodes but are not yet routinely available.

Recommendation	**Do not offer CT of the pelvis to men with low- or intermediate-risk localised prostate cancer (see table 17). [2008]**
Qualifying statement	There is not enough evidence to support the routine use of CT in men with intermediate-risk disease and it is considered inferior to MRI in this clinical situation.

Clinical evidence (2008)

No studies measuring the impact of diagnostic imaging on patient outcomes were found; instead most studies were of diagnostic test accuracy.

Two studies, reviewed in 'Improving outcomes in urological cancers service guidance' (NICE 2002), showed better staging accuracy with MRI than with CT. Other systematic reviews have considered the staging accuracy of MRI (Engelbrecht *et al*. 2002; Sonnad *et al*. 2001) and CT (Abuzallouf *et al*. 2004) separately.

There was contradictory evidence, from small observational studies, about the benefit of adding of MRS to MRI

There was consistent evidence, from observational studies, that MRI tumour stage was a prognostic factor for PSA relapse (Cheng *et al*. 2003; D'Amico *et al*. 2000; Nguyen *et al*. 2004; Pucar *et al*. 2004). One of the studies (D'Amico *et al*. 2000), however, concluded that MRI tumour staging only added clinically meaningful information for men at intermediate pre-treatment risk of PSA relapse. MRI tumour stage did not stratify PSA failure risk well enough to guide clinical decision making for other patients.

Clinical question: Does staging with MRI improve outcomes in men with prostate cancer?

Clinical evidence (see also full evidence review) (2014)

The evidence is summarised in Table 18.

Evidence statements

Biochemical recurrence-free survival

One study (Lavery *et al*. 2011) provided very low quality evidence of no significant difference in the proportion of patients experiencing biochemical recurrence between those which had undergone imaging and those which had not (p=0.50). However, the study was not limited only to those patients who underwent MRI (18%) and included patients who had received computerised tomography (81%) and bone scans (73%), with many patients receiving more than one type of imaging.

Overall survival, treatment-related morbidity, and health-related quality of life

No studies reported overall survival, treatment-related morbidity, or health-related quality of life.

Update 2014

Table 18: GRADE profile: Does staging with MRI improve clinical outcomes in men with prostate cancer?

Quality assessment							No. of events		Effect			Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imaging	Clinical staging only	Relative risk	95% CI	Absolute	
Biochemical recurrence (median follow-up 13.6 months)												
1	Cohort	None	None	Very serious[1]	Serious[2]	None	5 / 328 (1.5%)	3 / 349 (0.9%)	1.77	(0.43 – 7.36)	7 more per 1,000 (from 5 fewer to 55 more)	VERY LOW

1 The imaging group included patients who had undergone CT and/or bone scans instead of MRI. Only 18% of patients had undergone MRI.
2 Only eight patients in total experienced biochemical recurrence.

Update 2014

Cost-effectiveness evidence (see also full evidence review) (2014)

A literature review of published economic evidence identified one relevant paper by Stadlbauer *et al*. 2012. Stadlbauer *et al*. 2012 considered a German and Austrian health care setting and is written in German. Typically, non-English language studies are excluded from evidence reviews but, given the paucity of economic evidence in this area, an exception was made. The study included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis. The primary results of the analysis by Stadlbauer *et al*. 2012 are summarised in the modified Table 19.

No further health economic analysis was undertaken for this topic because other topics were deemed to be of greater economic importance and were thus given greater priority.

Study quality and results

Stadlbauer *et al* was considered to be only partially applicable to the guideline because it was not set in the UK (study considered a German and Austrian health care setting). In addition, it is unclear whether discounting has been considered in the analysis as it has not been reported. Likewise, the modelled time horizon was not reported, although it is presumed to cover the patient's expected lifetime.

Potentially serious limitations were also identified with the study. Further sensitivity analysis could have been conducted (particularly probabilistic sensitivity analysis). Furthermore, it was difficult to verify that the data inputs were drawn from the best available evidence because of insufficient detail provided in the report (a problem that was exacerbated by the report being written in a non-English language).

Evidence statements

The results from Stadlbauer *et al*. 2012 show staging with MR imaging to be cost-effective in all modelled scenarios. Furthermore, in the majority of scenarios, MR imaging was found to be dominant i.e. more effective and less costly than standard clinical staging.

However, the study setting and potential methodological problems limit the applicability of these otherwise strong results. Thus, it is difficult to draw any firm conclusions about the decision problem under consideration by using the results of this analysis and the cost-effectiveness of MRI staging remains, to a large degree, uncertain.

Update 2014

Table 19: Modified GRADE table showing the included evidence (Stadlbauer *et al*. 2012) comparing methods of clinical staging

Study	Population	Comparators	Costs	Effects	Incremental costs	Incremental effects	ICER	Uncertainty	Applicability and limitations
Stadlbauer *et al*. 2012	Hypothetical cohort of patients with confirmed prostate cancer	Therapy without MR staging	Per patient cost: €18,759	12.191 QALYs	Reference case			One-way and multi-way sensitivity analyses were conducted on variables of interest to the authors. MR staging was found to be dominant in all modelled scenarios with the exception of one analysis where the cost of prostate surgery was substantially reduced. However, even in this scenario MR staging was still cost-effective with an ICER of €3,245 per QALY.	Partly applicable. Potentially serious limitations.
		Therapy with MR staging	Per patient cost: €16,125	12.289 QALYs	-€2,635	0.099 QALYs	Therapy with MR staging is dominant.		
	Comments: Study was written in the German language and would not typically be included in the evidence review. However, given the absence of any other papers in the area, an exception has been made. Possible that some errors were made in translating the document.								

Recommendations	No recommendations were made
Relative value placed on the outcomes considered	Overall survival, biochemical recurrence-free survival, treatment related morbidity and health related quality of life were considered the most important outcomes to identifying if staging with MRI improves outcomes in men with prostate cancer. Of these outcomes, only biochemical recurrence-free survival was reported.
Quality of the evidence	The evidence for biochemical recurrence-free survival was assessed by GRADE as very low to low quality. A variety of limitations were identified with the evidence. Only 18% of patients had undergone MRI, the rest had received a CT scan, bone scans or both. This made it difficult to extrapolate the results for MRI to the whole population. In addition the study used endorectal coil MRIs which are no longer commonly used. Only low risk patients were included in the study, so the effect of staging with MRI on men within other risk groups was unclear. The median follow-up was very short (14 months), so there was uncertainty of the relative benefits and disbenefits of imaging versus clinical staging. There was also a lack of precision – the study was not powered to detect a statistically significant difference between interventions as only a total of eight patients had biochemical recurrence.
Trade-off between clinical benefits and harms	The GDG agreed that the limitations of the evidence and the lack of useful outcomes reported, meant it was not possible to make recommendations.
Other considerations	The GDG agreed it was not possible to recommend further research in this area because the trial would need to include a comparative arm of patients who did not have MRI. This could not be ethically recruited.

Update 2014

Clinical question: In which patients with prostate cancer will MRI staging alter treatment?

Clinical evidence (see also full evidence review) (2014)

Study quality and results

Four studies reported change in management following MRI, 23 reported change in staging following MRI, and eight reported the diagnostic accuracy of both clinical and MRI staging, using prostatectomy as reference standard. All studies were of low to very low quality evidence, with most (96%) considered unrepresentative of the patients who would receive MRI in practice. Many (68%) of the studies also used MRI as the reference standard which may not have classified the target condition correctly. A number of pre-specified sub-groups were available for analyses.

Evidence statements

Change in management

Two studies found a change in the management of radiotherapy strategy following MRI in 31% and 9% of patients. Two further studies found a change in surgical procedure in 44% and 30% of patients following MRI respectively.

Change in stage

All studies found reported MRI to result in up-staging of a proportion of their patients, ranging from at least 5% to 100% of all patients. Where reported, MRI also resulted in down-staging of between 5% and 19% of patients.

In studies of patients with clinically localised disease, the number of patients staged as T3 increased from none to 14% - 61% at MRI (where reported). In five (46%) of the studies all patients clinically staged as T1 were up-staged, some of which became stages T3a and T3b on MRI.

One study reported results for patients found to have stage T2 and T3 at prostatectomy; of 41 stage T2 patients, 63% and 83% were correctly staged clinically and by MRI respectively. Of the 21 stage T3 patients, 0% and 33% were correctly staged clinically and MRI respectively (Brown *et al*. 2009).

One study (Cirillo *et al*. 2008) reported the change in stage at MRI for different risk groups. Of the 82 low risk patients (PSA ≤ 10 ng/ml or Gleason 2-6), 34% were re-staged (32% up-staged and 2% down-staged). Of 44 intermediate risk patients (PSA 10-20 ng/ml or Gleason 7), 48% were re-staged (43% up-staged and 5% down-staged). Of 17 high risk patients (PSA > 20 ng/ml or Gleason 8-10), 65% were re-staged (47% up-staged and 18% down-staged).

One study only included patients with PSA < 10 ng/ml and found that all 56 were staged as T2 at DRE, while at TRUS 35 (63%) were found to be T2 and 21 (38%) were T3 (Presti *et al*. 1996). However at MRI, 19 (34%) were staged as T2 and 37 (66%) were staged as T3.

One study reported results for patients with Gleason 6 or 7-10 at biopsy (Brown *et al*. 2009). Of the 30 patients with Gleason score of 6, 21 (70%) versus 0 were staged as T1, 9 (30%) versus 26 (87%) were staged as T2, and 0 versus 4 (13%) were staged as T3 clinically or by MRI respectively. Of the 32 patients with Gleason score of 7-10, 15 (47%) versus 0 were staged as T1, 17 (53%) versus 22 (69%) were staged as T2, and 0 versus 10 (31%) were staged as T3 clinically or by MRI respectively.

Update 2014

Diagnostic accuracy

Four studies found that MRI was not consistently more sensitive, specific or accurate than staging by DRE or TRUS. Six studies found MRI to be more sensitive than clinical staging in identifying patients with extracapsular extension (stage T3a), but not consistently more specific or accurate. MRI was not consistently more sensitive, specific or accurate than clinical staging in identifying patients with seminal vesicle invasion (stage T3b).

Three studies of patients with clinically localised disease found MRI to be more sensitive than clinical staging when identifying extracapsular extension or seminal vesicle invasion, but not consistently more specific or accurate. One study (Vapnek *et al*. 1994) found MRI to have higher sensitivity but lower specificity than DRE or TRUS for overall staging of prostate cancer, while another (Bates *et al*. 1997) found MRI to have higher accuracy.

Two studies only included patients with PSA < 10 ng/ml; one found the overall accuracy of staging to be the same between MRI and TRUS, while both found MRI to be more sensitive but less specific than TRUS when identifying extracapsular extension and less sensitive when identifying seminal vesicle invasion but not consistently more specific (Presti *et al*. 1996; Novis *et al*. 2011). Another study (Sanchez-Chapado *et al*. 1997) conducted a subgroup analysis by PSA level and found MRI to be more sensitive than TRUS in identifying both extracapsular extension and seminal vesicle invasion in patients with either PSA > 17 ng/ml or PSA < 10 ng/ml.

Two studies only included patients with Gleason ≤ 6; one found MRI to be more sensitive but less specific than TRUS when identifying extracapsular extension and less sensitive when identifying seminal vesicle invasion but of similar specificity (Novis *et al*. 2011). The other

found MRI to have the same rate of false positives as clinical staging when identifying stage T3-T4 disease (Ploussard *et al*. 2011).

Shiavina *et al*. (2011) only included intermediate- and high-risk patients and found MRI to be more sensitive but less specific than clinical staging when identifying extracapsular extension, and to be more sensitive but have the same specificity when identifying seminal vesicle invasion.

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. No further economic modelling was undertaken because identifying those patients with prostate cancer in whom MRI staging will alter management was a clinical issue and therefore not appropriate for modelling.

Recommendations	**Consider multiparametric MRI, or CT if MRI is contraindicated, for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. [new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of change in stage and change in management to be the most important because these determine treatment options and the treatment plan. The outcome of diagnostic accuracy was also considered important. However the GDG noted that most studies reporting this outcome were over 10 years old, and consequently used old technologies. Those studies which were contemporary only had small patient numbers. In addition the studies reporting diagnostic accuracy were limited solely to patients who had surgery, thereby skewing the population and the interpretation of the evidence. Consequently the GDG decided to put less weight to the data on diagnostic accuracy.
Quality of the evidence	The evidence for change in management was assessed as low quality. The evidence on change in stage was assessed as very low quality. The GDG noted that the studies did not report the time between staging and the reference standard, meaning the stage of disease could have progressed during this time. In addition, the exclusion and inclusion criteria created a study population bias in the data, thereby causing potential difficulties when interpreting these data.
Trade-off between clinical benefits and harms	The GDG noted, based on the clinical evidence, that performing MRI in men with biopsy confirmed prostate cancer, can provide additional staging information that may affect treatment options. The GDG agreed that the staging information provided by MRI could result in a tumour being either downstaged or upstaged, but the accuracy of this was uncertain. The GDG acknowledged that if the information provided by MRI resulted in a T3 tumour being incorrectly downstaged to T2, the treatment intent may be altered from radiotherapy to surgery inappropriately. However the clinical experience of the GDG was that the likelihood of this happening was low. Conversely if the information provided by MRI resulted in a T2 tumour being incorrectly upstaged to T3, the treatment intent may be altered to radiotherapy or hormone treatments, instead of surgery. As a consequence, the patient would be confined to the morbidity associated with these treatment options. However, the GDG were not able to quantify the likelihood of this happening.

Update 2014

	The GDG weighed the risk of potentially downstaging a tumour (resulting in more treatment options) against the risk of potentially upstaging a tumour (resulting in reduced treatment options). Given that the GDG believed the likelihood of downstaging to be low and were not able to quantify the likelihood of upstaging the GDG agreed to recommend the use of MRI for staging to assist treatment decisions.
Trade-off between net health benefits and resource use	The GDG noted that the published economic evidence had shown treatment with MRI staging to be more effective and less costly than treatment without MRI staging. However, the GDG acknowledged that the study was only partially applicable and had serious limitations. Consequently the GDG agreed there was uncertainty over the results of this analysis and that they could only recommend MRI for staging be considered.

Update 2014

3.313 Imaging for M-staging

Isotope bone scans can be used to look for bone metastases at the time of presentation. The positivity rate for bone scans increases with PSA or Gleason score.

Recommendation	**Do not routinely offer isotope bone scans to men with low-risk localised prostate cancer. [2008]**
Qualifying statement	This recommendation is supported by case series evidence and will reduce unnecessary investigation.

Clinical evidence (2008)

Two systematic reviews (Abuzallouf *et al*. 2004 and NICE 'Improving outcomes in urological cancers' service guidance, 2002) looked at the role of radioisotope bone scans in the staging of men with newly diagnosed prostate cancer. Abuzallouf and co-workers summarised bone scan results by serum PSA level in men with newly diagnosed prostate cancer. Serum PSA level and risk of a positive bone scan were strongly correlated. The other review (NICE, 2002) concluded that PSA level was the best means of identifying those at risk of a positive bone scan and that men with PSA less than 10 ng/ml were unlikely to have a positive bone scan.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Recommendation	**Offer isotope bone scans when hormonal therapy is being deferred through watchful waiting to asymptomatic men who are at high risk of developing bone complications. [2008]**
Qualifying statement	In the absence of any evidence there was GDG consensus that making this recommendation would reduce the risk of patients developing spinal cord compression.

Clinical evidence (2008)

Searches found no direct evidence about the influence of imaging on the timing of systemic treatment or frequency of clinical follow-up in men for whom radical treatment is not intended. Small case series (Noguchi *et al*. 2003; Yamashita *et al*. 1993; Knudson *et al*. 1991) reported outcomes in men with positive bone scans at presentation. Two of these series (Noguchi *et al*. 2003; Knudson *et al*. 1991) found extensive disease on bone scan was an adverse prognostic factor for survival. There is observational evidence (Bayley, 2004; Venkitaraman,

2007) that extensive disease on bone scan is an independent risk factor for spinal cord compression in men without functional neurological impairment.

Cost-effectiveness evidence (2008)

The literature search identified 213 potentially relevant papers. One of these studies was obtained for appraisal but it did not contain an economic evaluation. No economic modelling was attempted because there was considered to be insufficient clinical information on which to base a model.

3.3.4 Role of PET in staging prostate cancer

Positron-emission tomography (PET) imaging using the radiopharmaceutical agent 18-FDG does not reliably show primary prostate cancer. This is because of the relatively low metabolic activity in tumours which are slow-growing and because the radiopharmaceutical agent accumulates in the bladder, obscuring the prostate. Newer positron-emitting tracers are under evaluation. These include 11-C acetate which has a high specificity for prostate cancer 18-F choline or 11-C choline.

Recommendation	**Do not offer positron emission tomography imaging for prostate cancer in routine clinical practice. [2008]**
Qualifying statement	There was a lack of evidence to support the use of PET imaging.

3.4 Nomograms

A nomogram is a statistically derived tool which is used to describe the likely course of a disease using known variables such as diagnostic findings, age and treatment options. Nomograms have been developed from outcome data on large groups of men with prostate cancer. Using predictive factors such as T-stage, Gleason score, PSA and histology results they can be used to estimate the risk of metastatic spread, lymph node involvement or recurrence following treatment. There is a wide variation in incidence rates between North America and the UK so that a nomogram developed in a screened population in the USA may not be wholly relevant to an unscreened population in this country and therefore need to be used with caution. Most nomograms in current use have been developed on patient groups outside the UK.

Recommendation	**Nomograms may be used by healthcare professionals in partnership with men with prostate cancer to:** • **aid decision making** • **help predict biopsy results** • **help predict pathological stage** • **help predict risk of treatment failure. [2008]**
Qualifying statement	There is good quality evidence to support this recommendation.
Recommendation	**When nomograms are used, clearly explain the reliability, validity and limitations of the prediction. [2008]**
Qualifying statement	In the absence of evidence of improved outcomes, there was GDG consensus that nomograms are of value in explaining the probable clinical course to patients.

Clinical evidence (2008)

There is good evidence from observational studies (see evidence review), largely from outside the UK, that nomograms can identify risks for men with prostate cancer. Most

nomograms have been developed for use in men with clinically localised disease who are candidates for radical prostatectomy, and these are also the most widely validated. Although only one UK validation study was found, some nomograms have been validated in other western European countries.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

3.5 References

2008

Abuzallouf S, Dayes I & Lukka H (2004) Baseline staging of newly diagnosed prostate cancer: a summary of the literature (DARE provisional record). Journal of Urology, 171: 2122–2127.

Bayley AJ, Catton CN, Haycocks T, Kelly V, Alasti H, Bristow R, Catton P, Crook J, Gospodarowicz MK, McLean M, Milosevic M & Warde P (2004) A randomized trial of supine vs. prone positioning in patients undergoing escalated dose conformal radiotherapy for prostate cancer. Radiotherapy & Oncology, 70: 37–44.

Borden LS, Wright JL, Kim J, Latchamsetty K & Porter CR (2006) An abnormal digital rectal examination is an independent predictor of Gleason >/=7 prostate cancer in men undergoing initial prostate biopsy: a prospective study of 790 men. BJU Int 99(3):559–63.

Cheng GC, Chen MH, Whittington R, Malkowicz SB, Schnall MD, Tomaszewski JE & D'Amico AV (2003) Clinical utility of endorectal MRI in determining PSA outcome for patients with biopsy Gleason score 7, PSA <or=10, and clinically localized prostate cancer. Int J Radiat.Oncol Biol.Phys., 55: 64–70.

D'Amico AV, Whittington R, Malkowicz B, Schnall M, Schultz D, Cote K, Tomaszewski JE & Wein A (2000) Endorectal magnetic resonance imaging as a predictor of biochemical outcome after radical prostatectomy in men with clinically localized prostate cancer. J Urol, 164: 759–763.

Department of Health (2002) The NHS Cancer Plan. Avaliable from www.dh.gov.uk.

Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM & Kleijnen J (2006) Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. [Review] [42 refs]. J Urol, 175: 1605–1612.

Engelbrecht MR, Jager GJ, Laheij RJ, Verbeek AL, van Lier HJ & Barentsz JO (2002) Local staging of prostate cancer using magnetic resonance imaging: a meta-analysis. Eur Radiol., 12: 2294–2302.

Garzotto M, Collins L, Priest R, Spurgeon S, Hsieh YC, Beer TM & Mori M (2005) Nomogram for the prediction of high-grade prostate cancer on ultrasoundguided needle biopsy. J Clin Oncol, 23: 408S.

Gleave ME, Coupland D, Drachenberg D, Cohen L, Kwong S, Goldenberg SL & Sullivan LD (1996) Ability of serum prostate-specific antigen levels to predict normal bone scans in patients with newly diagnosed prostate cancer. Urology, 47: 708–712.

Katagiri H, Takahashi M, Inagaki J, Sugiura H, Ito S & Iwata H (1999) Determining the site of the primary cancer in patients with skeletal metastasis of unknown origin: a retrospective study. Cancer, 86: 533–537.

Konski A *et al*. (2006) Using decision analysis to determine the cost-effectiveness of intensity-modulated radiation therapy in the treatment of intermediate riak prostate cancer. International Journal of Radiation Oncology, Biology Phsyics 66(2): 408-415.

Knudson G, Grinis G, Lopez-Majano V, Sansi P, Targonski P, Rubenstein M, Sharifi R & Guinan P (1991) Bone scan as a stratification variable in advanced prostate cancer. Cancer, 68: 316–320.

Krejcarek SC, Chen MH, Renshaw AA, Loffredo M, Sussman B & D'Amico AV (2007) Prediagnostic prostate-specific antigen velocity and probability of detecting high-grade prostate cancer. Urology, 69: 515–519.

Lin K, Szabo Z, Chin BB & Civelek AC (1999) The value of a baseline bone scan in patients with newly diagnosed prostate cancer. Clin Nucl Med, 24: 579–582.

Nam RK, Toi A, Klotz LH, Trachtenberg J, Jewett MA, Loblaw A, Pond GR, Emami M, Sugar L, Sweet J & Narod SA (2006) Nomogram prediction for prostate cancer and aggressive prostate cancer at time of biopsy: utilizing all risk factors and tumor markers for prostate cancer. Can J Urol, 13 Suppl 2: 2–10.

National Institute for Clinical Excellence (2002). Guidance on cancer services improving outcomes in urological cancers. The manual. London: National Institute for Clinical Excellence.

National Institute for Health and Clinical Excellence (2005) Referral guidelines for suspected cancer. NICE clinical guideline no. 27. London: National Institute for Health and Clinical Excellence.

Nguyen PL, Whittington R, Koo S, Schultz D, Cote KB, Loffredo M, Tempany CM, Titelbaum DS, Schnall MD, Renshaw AA, Tomaszewski JE & D'Amico AV (2004) Quantifying the impact of seminal vesicle invasion identified using endorectal magnetic resonance imaging on PSA outcome after radiation therapy for patients with clinically localized prostate cancer. Int J Radiat.Oncol Biol.Phys., 59: 400–405.

Noguchi M, Kikuchi H, Ishibashi M & Noda S (2003) Percentage of the positive area of bone metastasis is an independent predictor of disease death in advanced prostate cancer. Br J Cancer, 88: 195–201.

Oesterling JE (1993) Using PSA to eliminate the staging radionuclide bone scan. Significant economic implications. Urol Clin North Am, 20: 705–711.

O'Sullivan JM, Norman AR, Cook GJ, Fisher C & Dearnaley DP (2003) Broadening the criteria for avoiding staging bone scans in prostate cancer: a retrospective study of patients at the Royal Marsden Hospital. BJU Int, 92: 685–689.

Partin AW, Mangold LA, Lamm DM, *et al*. (2001) Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology 58:843.

Prostate Cancer Risk Management Programme (2006) Undertaking a trans-rectal ultrasound guided biopsy of the prostate. ISBN 9781844630417. Available online at http://www.cancerscreening.nhs.uk/prostate/pcrmp01.pdf.

Pucar D, Koutcher JA, Shah A, Dyke JP, Schwartz L, Thaler H, Kurhanewicz J, Scardino PT, Kelly WK, Hricak H & Zakian KL (2004) Preliminary assessment of magnetic resonance spectroscopic imaging in predicting treatment outcome in patients with prostate cancer at high risk for relapse. Clinical Prostate Cancer, 3: 174–181.

Sonnad SS, Langlotz CP & Schwartz JS (2001) Accuracy of MR imaging for staging prostate cancer: a meta-analysis to examine the effect of technologic change. Acad Radiol., 8: 149–157.

Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, Feng Z, Parnes HL & Coltman CA (2006) Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial.[see comment]. J Natl Cancer Inst, 98: 529–534.

Vandecandelaere M, Flipo RM, Cortet B, Catanzariti L, Duquesnoy B & Delcambre B (2004) Bone metastases revealing primary tumors. Comparison of two series separated by 30 years. Joint Bone Spine, 71: 224–229.

Venkitaraman R, Sohaib SA, Barbachano Y, Parker CC, Khoo V, Huddart RA Horwich A & Dearnaley DP (2007) Detection of Occult Spinal Cord Compression with Magnetic Resonance Imaging of the Spine. Clin Oncol (R Coll.Radiol.).

Wymenga LF, Boomsma JH, Groenier K, Piers DA & Mensink HJ (2001) Routine bone scans in patients with prostate cancer related to serum prostate-specific antigen and alkaline phosphatase. BJU Int, 88: 226–230.

Yamashita K, Denno K, Ueda T, Komatsubara Y, Kotake T, Usami M, Maeda O, Nakano S & Hasegawa Y (1993) Prognostic Significance of Bone Metastases in Patients with Metastatic Prostate-Cancer. Cancer, 71: 1297–1302.

2014

Bates TS, Gillatt DA, Cavanagh PM, *et al*. (1997). A comparison of endorectal magnetic resonance imaging and transrectal ultrasonography in the local staging of prostate cancer with histopathological correlation. British Journal of Urology 79(6): 927-932.

Belas O, Klap J, Cornud F, *et al*. (2012). Prebiopsy multiparametric MRI of the prostate: the end of randomized biopsies? Prog.Urol. 22 (10): 583-589.

Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C et al. Radical prostatectomy versus watchful waiting in early prostate cancer. 2011:1708-1717

Bollito E, De Luca S, Cicilano M, *et al*. (2012). Prostate cancer gene 3 urine assay cutoff in diagnosis of prostate cancer: a validation study on an Italian patient population undergoing first and repeat biopsy. Anal Quant Cytol Histol 34: 96-104.

Brown JAR (2009). Impact of preoperative endorectal MRI stage classification on neurovascular bundle sparing aggressiveness and the radical prostatectomy positive margin rate. Urologic Oncology: Seminars and Original Investigations 27(2): 174-179.

Campos-Fernandes JL, Bastien L, Nicolaiew N, *et al*. (2009). Prostate cancer detection rate in patients with repeated extended 21-sample needle biopsy. Eur Urol 55: 600-606.

Cirillo S, Petracchini M, Bona CM, *et al*. (2008). Comparison of endorectal magnetic resonance imaging, clinical prognostic factors and nomograms in the local staging of prostate cancer patients treated with radiotherapy. Tumori 94(1): 65-69.

Delongchamps NB, Peyromaure M, Schull A, *et al*. (2013). Prebiopsy Magnetic Resonance Imaging and Prostate Cancer Detection: Comparison of Random and Targeted Biopsies. J.Urol. 189 (2): 493-499.

Eichler K, Hempel S, Wilby J, *et al*. (2006) Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol. May; 175(5): 1605-12.

Haffner J, Lemaitre L, Puech P, *et al*. (2011). Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. BJU International 108: t-8.

Lavery HJ, Brajtbord JS, Levinson AW, *et al*. (2011). Unnecessary imaging for the staging of low-risk prostate cancer is common. Urology 77(2): 274-278.

Update 2014

Lee BH, Hernandez AV, Zaytoun O, *et al*. (2011). Utility of percent free prostate-specific antigen in repeat prostate biopsy. Urology 78: 386-391.

Morelli G (2009). Role of elastosonography and prostatic contrast-enhanced power-doppler ultrasound with 5-phosphodiesterase inhibitors in rebiopsy of patients with elevated PSA. Journal of Sexual Medicine Conference (var.pagings): December.

Mowatt G, Scotland G, Boachie C, *et al*. (2013). Systematic review of the diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen.

Naya Y, Ayala AG, Tamboli P, *et al* (2004). Can the number of cores with high-grade prostate intraepithelial neoplasia predict cancer in men who undergo repeat biopsy? Urology, 63, 503-508.

Nelson A, Harvey R, Parker R, *et al*. Repeat Prostate Biopsy Strategies after Initial Negative Biopsy: Meta-Regression Comparing Cancer Detection of Transperineal, Transrectal Saturation and MRI Guided Biopsy. Plos One 8 (2):e57480, 2013.

Novis MI, Baroni RH, Cerri LM, *et al*. (2011). Clinically low-risk prostate cancer: Evaluation with transrectal doppler ultrasound and functional magnetic resonance imaging. Clinics 66(1): 27-34.

Oxley JD and Sen C (2011). Error rates in reporting prostatic core biopsies. Histopathology 58(5): 759-765.

Park BK, Park JW, Park SY, *et al*. (2011). Prospective evaluation of 3-T MRI performed before initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-specific antigen and no previous biopsy. American Journal of Roentgenology 197: W876-W881.

Ploussard G, Nicolaiew N, Marchand C, *et al*. (2013). Risk of repeat biopsy and prostate cancer detection after an initial extended negative biopsy: longitudinal follow-up from a prospective trial. BJU International 111(6): 988-996 (secondary to Campos-Fernandez *et al*. 2009).

Ploussard G, Xylinas E, Durand X, *et al*. (2011). Magnetic resonance imaging does not improve the prediction of misclassification of prostate cancer patients eligible for active surveillance when the most stringent selection criteria are based on the saturation biopsy scheme. BJU International 108(4): 513-517.

Presti Jr JC, Hricak H, Narayan PA, *et al*. (1996). Local staging of prostatic carcinoma: Comparison of transrectal sonography and endorectal MR imaging. American Journal of Roentgenology 166(1): 103-108.

Remzi M, Dobrovits M, Reissigl A, *et al*. (2004). Can Power Doppler enhanced transrectal ultrasound guided biopsy improve prostate cancer detection on first and repeat prostate biopsy? Eur. Urol. 46(4): 451-456.

Sanchez-Chapado M, Angulo JC, Ibarburen C, *et al*. (1997). Comparison of digital rectal examination, transrectal ultrasonography, and multicoil magnetic resonance imaging for preoperative evaluation of prostate cancer. European Urology 32(2): 140-149.

Shiavina R (2011). Accuracy of endorectal MRI and dynamic contrast-enhanced MRI in the preoperative local staging of prostate cancer: A prospective study of 46 patients. Anticancer Research Conference(var.pagings): 1949.

Update 2014

Singh H, Canto EI, Shariat SF, *et al*. (2004). Predictors of prostate cancer after initial negative systematic 12 core biopsy. J Urol 171: 1850-1854.

Stadlbauer, A, Bernt R, Salomonowitz E, Plas E, Strunk G, Eberhardt K. “Health economics evaluation of magnetic resonance imaging for the staging of prostate cancer for Austria and Germany”. Rofo 184(6):729-36 2012

Taverna G, Morandi G, Seveso M, *et al*. (2011). Colour Doppler and microbubble contrast agent ultrasonography do not improve cancer detection rate in transrectal systematic prostate biopsy sampling. BJU International 108(11): 1723-1727.

Vapnek JM, Hricak H, Shinohara K, *et al*. (1994). Staging accuracy of magnetic resonance imaging versus transrectal ultrasound in stages A and B prostatic cancer. Urologia Internationalis 53(4): 191-195.

Wu AK, Reese AC, Cooperberg MR, *et al*. (2012). Utility of PCA3 in patients undergoing repeat biopsy for prostate cancer. Prostate Cancer Prostatic Dis. 15: 100-105.

Update 2014

4 Localised prostate cancer

4.1 Introduction

Prostate cancer may follow an aggressive course, similar to that of other cancers. However, many prostate cancers are indolent, and will have no impact on health, even without treatment. The natural history of prostate cancer diagnosed in the 1970s and 1980s has been well-described. For example, Albertsen *et al*. (2005), reporting the long-term outcome of watchful waiting, found that the 15-year prostate cancer mortality for men with a Gleason score of 6 was 18–30%, while their 15-year risk of death from other causes was 25–59%.

The detection of prostate cancers by prostate specific antigen (PSA)[f] testing has become increasingly common. PSA testing results in over-detection of cases that might not otherwise have been detected and their long-term natural history is not yet known. It also introduces a lead time (the time difference between detection by PSA and clinical presentation in the absence of PSA testing), which may be of the order of 10 years or more. It follows that the natural history of PSA-detected prostate cancer will appear more favourable than that of clinically detected prostate cancer from the pre-PSA testing era. This is an important consideration for men faced with the choice between conservative management and curative treatment. In comparison with those with clinically detected disease, men with PSA-detected cancers will have longer to endure any adverse effects of curative treatment, and longer to wait for any beneficial effect on survival to emerge.

4.2 Predictive factors and risk groups

Several factors have been shown to predict the risk of recurrence after treatment of localised prostate cancer. These include the Gleason score, the serum PSA level, and the T-stage. These predictive factors have been used to classify localised prostate cancer into risk groups, specifically:

- Low-risk PSA < 10 ng/ml and Gleason score ≤ 6, and clinical stage T1-T2a
- Intermediate-risk PSA 10–20 ng/ml, or Gleason score 7, or clinical stage T2b
- High-risk[g] PSA > 20 ng/ml, or Gleason score 8-10, or clinical stage ≥T2c (see Chapter 6 for more information on high-risk localised disease).

Update 2014

Recommendation	**Urological cancer MDTs should assign a risk category (see table 17) to all newly diagnosed men with localised prostate cancer. [2008]**
Qualifying statement	This recommendation is based on evidence from well-designed cohort studies.

Clinical evidence (2008)

There is consistent evidence from observational studies that biopsy, Gleason score and pre-treatment serum PSA level are independent risk factors for lymph node involvement, treatment failure and death from prostate cancer, in men with clinically localised prostate cancer. In these studies clinical tumour stage was an independent predictor of treatment failure but was not consistently associated with death from prostate cancer or lymph node involvement.

f For more information on PSA please see Appendix A.
g High-risk localised prostate cancer is also included in the definition of locally advanced prostate cancer

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Research recommendation	**Further research is required into the identification of prognostic indicators in order to differentiate effectively between men who may die with prostate cancer and those who might die from prostate cancer [2008].**
Why is this important	The greatest uncertainties in managing prostate cancer area round the identification of which cancers are of clinical significance and over the choice of radical treatment, and in which settings they are appropriate. With the diagnosis of prostate cancer being made more frequently in asymptomatic men, it is of growing importance to know which of these men are likely to benefit from aggressive treatment.

4.3 Treatment decision making

Given the uncertain, and often indolent, natural history of the disease, and the wide range of management options, treatment decision-making in localised prostate cancer is difficult. This is further complicated by the conflicting opinions of different doctors, and the risk of significant treatment-related toxicity. The NICE guidance on "Improving outcomes in urological cancers" (NICE 2002) recommended a multidisciplinary approach involving urologists, oncologists and specialist nurses to provide decision support.

The presence of lower urinary tract symptoms (LUTS) of bladder outlet obstruction, linked to high prostate volume and benign prostatic hyperplasia (BPH), might influence the man's choice of treatment option. As well as the clinical factors which define the risk group, the man's life-expectancy and his personal values need to be considered. For example, a fit 60 year old man with a typical life-expectancy of 25 years might be more likely to opt for a curative treatment than an older man with significant co-morbidities and/or a shorter life-expectancy. Similarly, a man who wanted to have the best chance of living as long as possible, and was prepared to accept side-effects, might be more likely to opt for curative treatment than a man who placed a higher value on his quality of life (see Chapter 2).

4.4 Initial treatment options

The treatment options for men with localised prostate cancer are:

- watchful waiting
- active surveillance
- radical prostatectomy (open, laparoscopic or robotically assisted laparoscopic)
- external beam radiotherapy (EBRT)
- brachytherapy (low and high dose rate)
- high intensity focused ultrasound (HIFU)
- cryotherapy.

4.4.1 Watchful waiting

Watchful waiting involves the conscious decision to avoid treatment unless symptoms of progressive disease develop. Those men who do develop symptoms of progressive disease are usually managed with hormonal therapy. This approach is most often offered to older men, or those with significant co-morbidities who are thought unlikely to have significant cancer progression during their likely natural life span.

Recommendation	**A member of the urological cancer MDT should review men with localised prostate cancer who have chosen a watchful waiting regimen and who have evidence of significant disease progression (that is, rapidly rising PSA level or bone pain). [2008]**
Qualifying statement	In the absence of evidence there was GDG consensus that this recommendation would avoid unnecessary investigations.

4.4.2 Active surveillance

The objective of active surveillance is to avoid unnecessary treatment of men with indolent cancers, by only treating those whose cancers show early signs of progression and may be life threatening. Whereas traditional watchful waiting in elderly or infirm men aims to avoid any treatment at all for as long as possible and excludes radical treatment options, active surveillance of younger, fitter men tries to target curative treatment on those likely to benefit. Active surveillance enables the man's risk to be re-assessed at regular intervals. In populations with low rates of PSA testing, risk categorisation may underplay the risk. If it were possible to identify a very low risk group of men with prostate cancer, these men would be ideally treated by active surveillance.

4.4.2.1 Who should have active surveillance?

The determination of a very low risk group of men ideally suited for active surveillance may take account of life expectancy, tumour stage, pathological characteristics, PSA levels and a family history of prostate cancer.

Clinical question: Which men with localised prostate cancer should be offered active surveillance?

Clinical evidence (see also full evidence review) (2014)

Study quality and results

Four analyses from three studies were found which reported on the effectiveness of relevant prognostic factors to predict biochemical progression or conversion-free survival. One of which was considered moderate quality (Selvadurai *et al*. 2013), one low quality (Khatami *et al*. 2007) and the other two very low quality evidence (Khatami *et al*. 2009; Klotz *et al*. 2010). All had a median follow-up of more than 5 years and only included patients with a Gleason score ≤ 7. Two of the studies assessed patients who had undergone active surveillance followed by radical treatment and were therefore not fully representative of those undergoing active surveillance in practice. It was also unclear whether one of the studies also included patients undergoing watchful waiting (Khatami *et al*. 2007). Two of the studies began recruitment in 1995 but neither provided information on when recruitment was closed. This coincides with a period of rapid increase in the number of PSA tests undertaken.

Update 2014

Evidence statements

PSA velocity

One moderate quality study found that a PSA velocity greater than 1.0 ng/ml/year significantly predicted later conversion to active treatment in patients undertaking active surveillance, in univariate and multivariate analyses (HR 1.4 95% CI 1.3-1.6 for the latter) (Selvadurai *et al*. 2013).

PSA level at diagnosis

One of two analyses of a single very low quality study (Khatami *et al*. 2009) found initial PSA level to be a significant predictor of biochemical progression in multivariate analyses (HR 1.86 95% CI 1.19-2.92). A second very low quality study (Klotz *et al*. 2010) found an initial PSA > 10 ng/ml did not predict conversion to active treatment in univariate analyses.

PSA density

One moderate quality study found that PSA density did not predict later conversion to radical treatment in an active surveillance cohort, in univariate or multivariate analyses (Selvadurai *et al*. 2013).

Free-to-total PSA

One low quality study found free-to-total PSA did not predict biochemical progression at radical prostatectomy in an active surveillance cohort, using a multivariate model (Khatami *et al*. 2007). A second moderate quality study (Selvadurai *et al*. 2013) found that ftPSA was a significant predictor of conversion to active treatment in both univariate and multivariate analyses (HR 0.91 95% CI 0.89-0.95 for the latter).

PSA doubling time (PSAdt)

One very low quality study found patients with PSAdt < 3 years to have 8.5-times greater risk of biochemical progression compared with patients with PSAdt ≥ 3 years. However, among patients with a PSAdt < 3 years, the absolute value of PSAdt (0-1, 1-2 or 2-3 years) was not predictive of biochemical failure after treatment (Klotz *et al*. 2010). Two further very low quality studies found conflicting results regarding PSAdt as a predictor of biochemical progression in multivariate models (accounting for different confouders) (Khatami *et al*. 2007; Khatami *et al*. 2009).

Update 2014

Total cancer length at biopsy

One low quality study found total cancer length at biopsy was not a significant predictor of biochemical progression at radical prostatectomy in multivariate analyses (Khatami *et al*. 2007).

Tumour volume

One very low quality study found tumour volume was not a significant predictor of biochemical progression in multivariate analyses (Khatami *et al*. 2009).

Gleason score at diagnosis

One very low quality study found Gleason score at diagnosis was not a significant predictor of biochemical progression in multivariate analyses (Khatami *et al*. 2009). Two further studies provided low quality evidence that Gleason score > 6 was a significant predictor of conversion to active treatment in univariate analyses, however, one study did not find it to be significant in multivariate analyses (Klotz *et al*. 2010; Selvadurai *et al*. 2013).

Clinical stage at diagnosis

Two studies provided low quality evidence that an initial T stage of 2a or greater significantly predicted later conversion to active treatment in patients undertaking active surveillance, in univariate analyses. However, Selvadurai *et al*. (2013) did not find it to be a significant predictor in multivariate analyses.

Biomarker Ki-67% expression

One very low quality study conducted multivariate analyses and found expression of biomarker Ki-67% to be a significant predictor of biochemical progression at radical prostatectomy in an active surveillance cohort (HR 2.49 95% CI 1.07-5.80) (Khatami *et al*. 2009).

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. No further economic analysis was undertaken partly because the selection of patients who are offered active surveillance is more of a clinical issue than an economic one. Furthermore, even if the topic was considered a high priority for economic analysis, the development of an economic model would have been hindered by the clinical evidence available. In particular, equivalent risk groups were not applied across clinical trials making it difficult to pool the clinical data by risk groups.

Recommendations	**Offer active surveillance as an option to men with low-risk localised prostate cancer for whom radical surgery or radiotherapy is suitable. [new 2014]** **Ensure that men:** • **are told about treatment options and their risks and benefits and** • **are aware that there is limited evidence for some treatment options and** • **are not unduly influenced by healthcare professional preference when selecting treatment options.** **[new 2014]** **Consider active surveillance for men with intermediate-risk localised prostate cancer who do not wish to have immediate radical treatment, in line with the recommendation on page 156. [new 2014]** **Do not offer active surveillance to men with high-risk localised prostate cancer. [2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of overall survival, progression-free survival, conversion-free survival and rates of conversion from active surveillance to other treatment to be the most relevant in identifying which men with localised prostate cancer should be offered active surveillance. The GDG were also interested to determine if there was a specific subgroup of men with low-risk localised prostate cancer who would particularly benefit from this treatment option.
Quality of the evidence	The quality of the evidence was low to very low based on a prognostic studies checklist and only comprised two prospective studies. The GDG noted the following limitations of the evidence: • an absence of clinically meaningful endpoints • high attrition rate • inclusion of men on watchful waiting in some studies In addition, because the duration of follow-up in the included studies was less than 10 years, it was difficult to accurately assess the outcomes of interest in men who had active surveillance. Given these limitations the GDG were unable to use the outcomes of interest when making recommendations. They noted that evidence on

Update 2014

	changes in PSA was reported in the trials appraised for this topic. In clinical practice these changes are used as surrogate predictors of progression. As a result, the GDG agreed to base their recommendations on these trials.
Trade-off between clinical benefits and harms	The GDG noted that the evidence had shown Gleason score did predict future outcome. It was acknowledged that whilst recommending active surveillance for men with low-risk localised disease would have the benefits of reducing over-treatment and associated morbidity, it was possible that some men may be under-treated. However the GDG agreed that the benefits outweighed the harms in this instance and consequently recommended that active surveillance should be a treatment option for men with low-risk localised prostate cancer who are suitable for radical treatment. It was noted that some men are currently given advice on treatment options based on their clinicians' preferences. The GDG agreed that this was not appropriate and that a recommendation should be made to address this issue, based on their clinical experience, that aligned with the existing Improving Outcomes in Urological Cancer Guidance (NICE, 2002) and best practice. The GDG acknowledged that whilst providing men with information on all treatment options may mean that extra support is needed to help with making a decision and to deal with the consequences of that decision; the benefits of informed decision making outweighed this. The GDG were also aware of upward migration in Gleason score following the International Society of Urological Pathology 2005 consensus meeting (Epstein *et al*, 2005). As a result of this a proportion of men who would have historically been classified as low-risk based on their Gleason score are now being classified as intermediate risk. The GDG took this change into account by recommending active surveillance is considered for men with intermediate-risk localised prostate cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. It was the opinion of the GDG that an increasing number of men would have active surveillance as a result of these recommendations. However, they agreed that any additional costs were likely to be offset by savings from a corresponding decrease in the number of men having radical treatment.
Other considerations	Based on the available evidence the GDG were not able to identify a specific subgroup of men with low-risk localised prostate cancer who would benefit from active surveillance. The GDG were aware of ongoing trials in this area, which when published, will hopefully lead to a better understanding of clinical outcomes. However these trials will not provide information to accurately risk stratify the outcome of active surveillance at diagnosis. Consequently the GDG agreed to recommend further research in this area.

Update 2014

1

Research recommendation	**Risk stratification using biomarkers and/or imaging should be compared to standard clinical risk predictors in men previously diagnosed with prostate cancer on long-term active surveillance. Outcomes of interest are overall survival, progression-free survival, rate of conversion from active surveillance to other treatment, conversion-free survival and health-related quality of life. [2014]**
Why is this important	The optimal strategy for active surveillance is not yet well defined. Currently many protocols employ repeated biopsies, which carry risk, but the use of other less invasive tests to predict the risk of progression, such as biomarkers and radiological findings, has not yet been fully explored

4.4.212 How should active surveillance be performed?

The intention of an active surveillance protocol is to indentify as early as possible those cancers that require radical treatment. There is currently no consensus as to the optimal protocol, but typically it involves frequent follow-ups with examinations, PSA testing, imaging and repeat biopsies. An effective active surveillance protocol would need to take account of outcomes such as overall and cancer-free survival. However it is recognised that long term outcome data may not be available.

Clinical question: What is the most effective follow-up protocol for active surveillance?

Clinical evidence (see also full evidence review) (2014)

Study quality and results

The literature searches identified no studies comparing the effectiveness of active surveillance protocols in use against one another. A systematic review (Dahabreh *et al*. 2012) was found which summarised the protocols from 16 cohorts of active surveillance in men with low risk or clinically localised (T1 or T2) prostate cancer (see Table 20). A survey of active surveillance protocols used by the cancer networks in England and Wales was undertaken to inform a Delphi consensus.

Evidence statements

Active surveillance protocols in use

A systematic review of the active surveillance protocols found that eligibility was typically based on Gleason score (12/16 studies), PSA level (10/16) and number of positive biopsy cores (8/16). Most studies used PSA kinetics, DRE and re-biopsy in the follow up of men on active surveillance.

Delphi consensus on active surveillance

The guideline development group felt that the variation in UK active surveillance protocols indicated a need for standardised protocol. However the group felt that due to the lack of published evidence about the effectiveness of active surveillance protocols any such recommendations could not be implemented without first seeking consensus within the prostate cancer community. For this reason the group decided to use a modified Delphi formal process (Strauss and Ziegler 1975) to seek consensus about the ideal active surveillance protocol for low risk localised prostate cancer. The guideline group invited 210 health professionals and patients to participate in the consensus process. In round one 152 respondents took part, 120 took part in round two, and 102 in round three. Details of the methods used and full results are given in Appendix C of the evidence review.

Following three rounds consensus (defined as agreement between at least two-thirds of respondents) was reached on several components of the active surveillance protocol (see Table 21).

Update 2014

Table 20: Eligibility Criteria and Follow-up Protocols in Studies of Active Surveillance in men with low risk or clinically localised (T1-T2) prostate cancer (Dahabreh *et al*. 2012)

				Eligibility Criteria			Follow up Protocol		
AS Cohort or Centre	**Country**	**Year Enrolment Began**	**Term Used in Original Article**	**Age (years)**	**Gleason score**	**PSA Level, µg/L**	**PSA Level or kinetics**	**DRE**	**Rebiopsy**
Baylor College of Medicine and Memorial Sloan-Kettering Cancer Center	USA	1984	EM, deferred therapy	NR	<7	NR	PSAV>0.75 µg/L/y	Used	Used
McGill University	Canada	1987	WW, AS	NR	NR	NR	Used but not specified	Used	Used
University of Connecticut Health Center	USA	1990	AS	NR	NR	NR	Used but not specified	Used	Used
Four tertiary care academic medical centres	USA	1991	AS	≤75	≤6	≤10	Used but not specified	Used	Used
University of Miami	USA	1991	WW, AS	≤80	≤6	≤15 , ≤10*	PSA increase of 25%-50% per year	Used	Used
University of California, San Francisco	USA	After 1991	AS	NR	≤6	<10	PSAV > 0.75 µg/L/y PSADT < 1 y	Used	Used
Royal Marsden Hospital	UK	1993	AS	NR	<3+ 4	≤20 , ≤15*	PSAV > 1.0 µg/L/y PSADT < 4 y	Used	Not routine
Johns Hopkins University	USA	1994	AS, EM with curative intent	NR	≤6	PSAD ≤ 0.15 µg/L/y	PSA kinetics were not used as triggers for intervention	Used	Used

				Eligibility Criteria			Follow up Protocol		
AS Cohort or Centre	**Country**	**Year Enrolment Began**	**Term Used in Original Article**	**Age (years)**	**Gleason score**	**PSA Level, µg/L**	**PSA Level or kinetics**	**DRE**	**Rebiopsy**
Toronto – Sunnybrook Regional Cancer Center	Canada	1995	WW, AS	NR	≤6 ≤3 + 4 (if age ≥70 y)	≤10 ≤15 (if age ≥70 y)	PSADT < 2 y Protocol changes in PSADT assessment or calculation in 1999 and after 2002. In 2005 the group developed a general linear mixed model to aid clinical decision making	Used	Used
Memorial Sloan-Kettering Cancer Center	USA	1997	AS	NR	No Gleason score 4 or 5	< 10	>10 µg/L	Used	Used
ProtecT	UK	2000	Active monitoring	NR	NR	NR	Used but not specified	Used	Not routine
Dana-Farber Cancer Institute	USA	2000	AS	NR	≤6 with no pattern 4	NR	Used but not specified	Used	Used
Kagawa Medical University	Japan	2002	AS	50-80	≤6	≤20	PSADT < 2y	NR	Used
Cleveland Clinic	USA	2004	Surveillance	NR	No Gleason score 4 or 5	≤10	Used but not specified	NR	Used
PRIAS	Multinational	2006	AS	NR	≤3 + 3	≤10 PSAD ≤ 0.2 µg/L/y	PSADT 0 - 3y	Used	Used
PASS	USA	2008	AS	NR	NR	NR	PSADT < 3y	Used	Used

*Abbreviations: AS, active surveillance; DRE, digital rectal examination; EM, expectant management; NR, not reported; PSA, prostate-specific antigen ;PSAV, PSA velocity; PSAD, PSA density; PSADT, PSA doubling time; WW, watchful waiting; *Different PSA criteria reported in different publications*

Table 21: Active surveillance (AS) protocol for low risk localised prostate cancer: consensus survey results

	Survey round		
	1	2	3
No prostate re-biopsy BEFORE enrolment on AS	x	//	-
Mp-MRI should be done BEFORE enrolment on AS	x	//	-
Routine prostate re-biopsy should be done during AS	x	//	-
Frequency and timing of routine re-biopsy during AS	x	x	†
Routine mp-MRI should be done during AS	x	x	x
Re-biopsy should be done following clinical/radiological changes	x	//	-
Mp-MRI should be done following clinical changes	x	//	-
MRI, PSA or DRE during AS are useful in deciding whether a re-biopsy should be done	//	-	-
PSA should be measured during AS	//	-	-
PSAv and PSAdt be should be calculated during AS	//	-	-
How often should PSA be measured during AS?	x	x	†
PSA can be monitored in primary care (under certain conditions)	x	x	//
DRE should be done during AS	//	-	-
How often should DRE be done during AS?	x	x	†
When could the frequency of AS be reduced?	x	x	x

Key: x consensus not reached; // consensus reached; † consensus on parts of this item; - item not included in survey round

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. Despite this being an area of high economic importance, further economic analysis was not undertaken primarily because of concerns about the feasibility of building a model in this area. The lack of clinical evidence available coupled with inconsistency amongst the active surveillance protocols used in studies makes it very difficult to pool and compare strategies.

<table>
<tr><td>Recommendations</td><td>Consider using the following protocol for men who have chosen active surveillance:
<table>
<tr><th>Timing</th><th>Tests[a]</th></tr>
<tr><td>At enrolment in active surveillance</td><td>Multiparametric MRI if not previously performed</td></tr>
<tr><td>Year 1 of active surveillance</td><td>Every 3–4 months: measure PSA[b]
Throughout active surveillance: monitor PSA kinetics[c]
Every 6–12 months: DRE[d]
At 12 months: prostate re-biopsy</td></tr>
<tr><td>Years 2–4 of active surveillance</td><td>Every 3–6 months: measure PSA[b]
Throughout active surveillance: monitor PSA kinetics[c]
Every 6–12 months: DRE [d]</td></tr>
<tr><td>Year 5 and every year thereafter until active surveillance ends</td><td>Every 6 months: measure PSA[b]
Throughout active surveillance: monitor PSA kinetics[c]
Every 12 months: DRE [d]</td></tr>
<tr><td colspan="2">a If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or rebiopsy
b May be carried out in primary care if there are agreed shared-care protocols and recall systems
c May include PSA doubling time and velocity
d Should be performedby a healthcare professional with expertise and confidence in performing DRE</td></tr>
</table>
[new 2014]</td></tr>
<tr><td>Relative value placed on the outcomes considered</td><td>The GDG considered the outcomes of overall survival, progression-free survival, biochemical disease-free survival, conversion free survival, surveillance-related morbidity, surveillance-related mortality, treatment-related morbidity, treatment-related mortality, adverse events and health-related quality of life to be the most important in determining the most effective active surveillance protocol.

The only outcome reported in the evidence reviewed was biochemical recurrence-free survival.</td></tr>
<tr><td>Quality of the evidence</td><td>The GDG noted that only one comparative study had been identified by the literature search. This reported the outcome of biochemical recurrence-free survival but was assessed by GRADE as very low quality.

They also noted the systematic review of published active surveillance protocols were mostly from outside the UK, making it difficult to extrapolate to the UK healthcare setting where PSA testing is less common and where the consequent stage migration has not occurred.

The GDG also noted that the results of the active surveillance protocol survey conducted across UK Cancer Networks demonstrated wide variations in the protocols used.

The GDG agreed that it was not possible to recommend a specific protocol</td></tr>
</table>

Update 2014

	for active surveillance based on this evidence as there was too much variation. They therefore decided to conduct a Delphi consensus exercise with stakeholders to see if it was possible to get consensus on what an active surveillance protocol should include. The results of the Delphi consensus exercise are very low quality evidence about the effectiveness of active surveillance protocol because they are based on opinion. The GDG acknowledged that consensus had not been achieved on certain elements of the protocol, particularly related to frequency and timing of tests/investigations. However the GDG decided that conducting further rounds of surveys was unlikely to resolve this. The GDG therefore agreed to recommend an active surveillance protocol which allowed flexibility in areas where consensus had not been achieved.
Trade-off between clinical benefits and harms	The GDG agreed that recommending a protocol for active surveillance would help to standardise current clinical practice and remove variation, which would benefit both men and clinicians and provide an audit standard for active surveillance. The GDG agreed that the protocol recommended was likely to result in a reduction in the frequency of prostate biopsies and the morbidity associated with this. In addition the recommended protocol may reduce hospital led follow-up. The GDG acknowledged that because the protocol would be based on the results of the Delphi consensus exercise, due to a lack of evidence from clinical trials, there was uncertainty over its effectiveness. However they considered the benefits of standardising practice would outweigh this potential harm.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. It was the opinion of the GDG, based on their clinical experience that the recommendations would lead to fewer biopsies being undertaken but an increase in the number of MRIs. However the GDG were unsure of the net effect because there is no consistency in the protocols used for active surveillance.
Other	The GDG acknowledged that there was uncertainty about how to interpret the results obtained from the tests recommended in the protocol. Because the Delphi consensus exercise and the evidence review had not looked at this issue, the GDG were not able to give specific guidance on what PSA changes or what findings on DRE should prompt a particular course of action. However, they agreed, based on their clinical experience that clinical or PSA changes should prompt expert re-assessment.

Update 2014

Recommendation	**Offer radical treatment men with localised prostate cancer who have chosen an active surveillance regimen and who have evidence of disease progression. [2008, amended 2014]** **The decision to proceed from an active surveillance regimen to radical treatment should be made in the light of the individual man's personal preferences, comorbidities and life expectancy. [2008]**
Qualifying statement	These recommendations are made on the basis of GDG consensus supported by cohort and observational studies.

Clinical evidence (2008)

A systematic review (Martin et al. 2006) compared definitions of disease progression and the rate at which men abandoned active surveillance. Individual studies defined disease progression using a combination of biochemical, histological and clinical criteria. Studies differed in their criteria for biochemical and histological progression. There was no evidence about the effect of definition of disease progression on outcomes.

The short follow-up and small sample sizes in these series meant relatively few disease progression events, and attempts to identify predictive factors for progression were unreliable A rapidly rising PSA was generally accepted as an indication for treatment, but there was no consensus on the definition of biochemical progression that should trigger radical treatment. High grade disease on prostate re-biopsy, increase in clinical tumour stage and the emergence of urinary symptoms were indications for intervention in some of the series.

Cost effectiveness evidence (2008)

The literature search on the indications for stopping active surveillance identified 53 potentially relevant papers, but none were obtained for appraisal as they did not include any economic evaluations. No economic modelling was attempted because there was considered to be insufficient clinical information on which to base a model.

4.4.3 Surgery versus radiotherapy

Radical prostatectomy involves removal of the entire prostate gland and seminal vesicles. Surgery has been traditionally performed by an open retropubic or perineal approach. The risks associated with surgery include incontinence, erectile dysfunction (see section 4.5) and the chance of involved surgical margins. Recently, laparoscopic or robotically assisted techniques have shortened inpatient stays and reduced blood loss. Radical prostatectomy is a major operation that is typically only offered to fitter men without co-morbidities.

External beam radiotherapy is the most common treatment in the UK for men diagnosed with localised prostate cancer. It is usually preceded by a period of hormonal therapy, and is given in daily fractions over 4–8 weeks as an outpatient. The side effects of this treatment can include alteration in urinary and bowel function and erectile dysfunction (see section 4.5).

Recommendations	**Offer radical prostatectomy or radical radiotherapy to men with intermediate-risk localised prostate cancer. [2008]** **Offer radical prostatectomy or radical radiotherapy to men with high-risk localised prostate cancer when there is a realistic prospect of long-term disease control. [2008]**
Qualifying statement	There is no strong evidence for the benefit of one treatment over another. Relatively little health gain is required for these interventions to become demonstrably cost-effective.

Clinical evidence (2008)

Radical prostatectomy

Evidence comes from a randomised trial comparing radical prostatectomy and watchful waiting (Bill-Axelson *et al*. 2005; Steineck *et al*. 2002), in men with localised, well to moderately-well differentiated prostate cancer. Overall mortality, within 10 years of follow-up, was lower in men treated with prostatectomy than in those managed with watchful waiting: 27.0% versus 32.0% respectively (Bill-Axelson *et al*. 2005). Similarly, the rate of death from prostate cancer within 10 years of follow-up was lower in the prostatectomy group than in the watchful waiting group (9.6% vs. 14.9% respectively). Erectile dysfunction and urinary incontinence, however, were significantly more likely in the prostatectomy group (Steineck *et al*. 2002).

Two small randomised trials compared prostatectomy with radiotherapy in men with locally advanced prostate cancer (Akakura *et al*. 2006) and in those with clinically localised prostate cancer (Paulson *et al*. 1982). The applicability of the trials is limited due to methodological

problems (Paulson *et al*. 1982; Akakura *et al*. 2006) and use of adjuvant and neoadjuvant hormonal therapy in all patients (Akakura *et al*. 2006).

Radical radiotherapy

No randomised trials comparing external beam radiotherapy with watchful waiting were found. Evidence about outcomes after external beam radiotherapy comes from observational studies, or from randomised trials comparing radiotherapy techniques. A systematic review (Nilsson *et al*. 2004) included 26 retrospective observational studies (17,018 patients) reported outcomes after conventional external beam radiotherapy. Cost-effectiveness evidence (2008) (see also Appendix D)

The literature search identified 1,532 papers that potentially estimated the cost-effectiveness of brachytherapy, cryotherapy, HIFU, radical prostatectomy, external beam radiotherapy, intensity modulated radiotherapy, watchful waiting and active surveillance for men with localised prostate cancer. One hundred and thirty-six papers were obtained for appraisal and four full economic evaluations were subsequently identified and reviewed (Horwitz *et al*. 1999; Hummel *et al*. 2003; Calvert *et al*. 2003, Konski *et al*. 2006 and Buron *et al*. 2007).

The first of these studies (Horwitz *et al*. 1999) compared 3D conformal radiotherapy with conventional techniques in a US setting, but was only available as an abstract and thus was not reviewed any further. The most recent study, by Konski *et al*. 2006 compared 3D conformal radiotherapy with intensity modulated radiotherapy (IMRT). The main limitation with this study was that differences in treatment effect were estimated using non-randomised studies, and few details of the literature search used to identify the non-randomised studies were provided. The remaining two studies were both performed in the UK (Hummel *et al*. 2003; Calvert *et al*. 2003). Hummel *et al*. (2003) assessed the costs and effects of a number of different treatment options, including active surveillance and radical prostatectomy, from a National Health Service (NHS) perspective. Health outcomes were expressed in terms of quality-adjusted life-years (QALYs) and a Markov model was used to assess the stream of costs and QALYs over a patient's lifetime. However, a core assumption within the analysis was that the treatment options did not differ in terms of altering the progression of the underlying prostate cancer, as little clinical evidence was available to prove otherwise. More specifically, no suitable randomised control trials (RCTs) were available with which to estimate the relative treatment effects. Thus, differences in treatment effect were only estimated in terms of expected side-effect profiles, although again, it should be noted that none of this evidence was derived from randomised trials.

While the baseline estimates suggested brachytherapy was cost-effective compared to active surveillance and radical prostatectomy, the authors concluded that this finding was not robust given the significant uncertainty surrounding the relative side effect profiles for the various treatment options. Moreover, different assumptions regarding the effect of treatment on the underlying prostate cancer also led to potentially different policy conclusions.

The economic evaluation by Calvert *et al*. (2003) compared policies of watchful waiting with radical prostatectomy in 60-year-old men with Gleason scores of 5–7[h]. Costs were considered from a NHS perspective and the analysis was based on a Markov model. Health outcomes were expressed in terms of life-years gained and QALYs, the latter by adjusting expected survival for changes in health-related quality-of-life in terms of the underlying prostate cancer and adverse effects of treatment such as incontinence and impotence.

The baseline results of the analysis suggested that watchful waiting was less costly and more effective than radical prostatectomy (that is, it produced more QALYs). However, it should be noted that the number of QALYs gained per patient was almost equivalent for the

h Calvert *et al*. (2003) did include a third treatment option, a selection-based management option using DNA-ploidy as a marker of disease progression. However, as this option was considered to be experimental, it is not expanded upon in this paper.

two management options suggesting that gains in survival attributable to radical prostatectomy were more than offset by increases in the incidence of post-operative complications. Moreover, none of the effectiveness evidence incorporated into the model was based on the results from RCTs, thus, it is difficult to have complete confidence in the robustness of the results.

The evaluation by Buron *et al*. (2007) compared the costs and benefits of (interstitial) brachytherapy with radical prostatectomy for men with a mean Gleason score of approximately 6. The evaluation was performed from a (French) societal perspective. The results suggested that the mean societal costs of the two treatment options were similar (Euros 8,000–8,700) but that their side-effect profiles differed, with some domains favouring radical prostatectomy, and others favouring brachytherapy. However, there were a number of significant limitations with the analysis: 1) changes in health-related quality-of-life were not measured using a utility-based instrument (meaning it is unclear which, if either treatment, was to be preferred on quality-of-life grounds); 2) patients in the study were not randomised to the treatment options and 3) the treatment options were assumed to be clinically equivalent in terms of the progression of the underlying prostate cancer.

In terms of developing the understanding of the cost-effectiveness of the treatment options for men with localised prostate cancer, there are arguably two main limitations with the existing literature. Firstly, only the evaluation by Hummel *et al*. (2003) attempted to assess the cost-effectiveness of more than two treatment options, when a number of other options exist. Secondly, none of the studies incorporates information from a more recently published RCT that compared radical prostatectomy versus watchful waiting (Bill-Axelson *et al*. 2005). Thus a new economic model was developed for this guideline that attempted to address these two issues.

De novo economic evaluation

The primary aim of this economic evaluation was to assess the cost-effectiveness of watchful waiting versus radical prostatectomy using published results from the single RCT. A secondary objective in the absence of RCT evidence, was to estimate how effective other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to be in order to be considered cost-effective, by conducting a threshold analysis on the number of additional QALYs that were required to achieve certain willingness-to-pay thresholds for a given value of one additional QALY. The economic evaluation was based on a Markov model, and performed from a NHS cost perspective. Health outcomes were expressed in terms of QALYs and the model was run over 20 1-year periods. Over the period, hypothetical patients could remain with localised disease, be free from prostate cancer, develop metastatic disease or die (from prostate cancer or other age-adjusted causes). The costs of treatment and the probability of adverse effects following treatment (and their associated impact on health-related quality-of-life [HRQoL] and cost) were amongst the variables included in the analysis. Information on the relative effectiveness of radical prostatectomy compared with watchful waiting was derived from Bill-Axelson *et al*. (2005). Cost and utility data were mostly derived from the published literature. The possibility and outcomes of adverse events were also included in the model.

Results

When the side-effects associated with the treatment strategies were excluded, radical prostatectomy was associated with incremental cost-effectiveness ratios (ICERs) of less than £10,000, both in terms of life-years gained and QALYs (Table 22). However, when the possibility and consequences of post-operative complications were included in the analysis, watchful waiting was shown to be the less costly and more effective option. That is, increases in life expectancy and increases in HRQoL associated with a slower progression of the underlying prostate cancer were more than offset by reductions in HRQoL as a result of surgery-related side effects. However, deterministic sensitivity analysis suggested that this

result was extremely sensitive to different assumptions regarding the probability of experiencing surgery-related side effects, their duration and their associated disutilities. Thus, it is difficult to attach much confidence to the results as small changes to the underlying parameters and assumptions arguably lead to different decisions regarding the most economically preferable management option.

Table 22: Baseline incremental cost-effectiveness ratios

	Cost	LY	QALYs1	QALYs2
WW	£6185	9.69	6.96	6.63
RP	£10,619	10.19	7.52	6.36
ICER		£8868	£7918	Dominated

RP, radical prostatectomy; WW, watchful waiting; ICER, incremental cost-effectiveness ratio

In QALYs1, there is 0 probability of complications following treatment whereas in QALYs2, the additional probabilities of urinary obstruction, urinary leakage and impotence are assumed.

The figure in bold represents the main baseline result. In this instance, RP is more costly and less effective than WW, thus it is 'dominated'.

Threshold analysis was conducted in order to see how effective, in terms of extra QALYs, other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to be in order for them to be cost-effective (compared to watchful waiting). The analysis showed that the remaining treatment options would need to produce between 0.07 and 0.28 additional QALYs compared to watchful waiting in order for them to be considered cost-effective at the £30,000 per additional QALY level[i] Table 23).

Table 23: Results from the threshold analysis over a 20 year period compared to watchful waiting using a willingness-to-pay for an extra QALY of £30,000.

Treatment	Expected cost of treatment	Required QALY increase*	Equivalent health gain in months**
External beam	£8,288	0.07	1
Brachytherapy	£10,992	0.16	2
HIFU	£12,188	0.20	2.4
Cryotherapy	£12,630	0.21	2.6
IMRT	£14,688	0.28	3.4

IMRT – intensity modulated radiotherapy; HIFU – high intensity focused ultrasound

**Required to achieve a cost per QALY gained of £30,000 compared with watchful waiting.*

***For example, external beam radiotherapy would have to produce 1 extra month of perfect health over a 20 year period compared to watchful waiting for it to be considered cost-effective, which is itself equivalent to 0.07 QALYs. This was calculated as follows: 1 day of perfect health = 1/365 = 0.002739. 0.07 QALYs/0.002739 = approximately 1 month.*

Summary

The results from this analysis suggest that the cost-effectiveness of radical prostatectomy is highly dependent on the choice of health outcomes included in the analysis. If only patient survival is considered, then radical prostatectomy is arguably cost-effective. However, when quality-of-life considerations with respect to both the underlying prostate cancer and treatment-related side effects are included, watchful waiting becomes a more desirable option both in terms of expected costs and quality-adjusted survival. This said, the sensitivity

i In the economic evidence for the 2008 recommendations, the 2008 GDG used a threshold of £30,000 per QALY to assess cost-effectiveness, which is the upper boundary of NICE's cost-effectiveness threshold. However, in the economic evidence for the 2014 recommendations, the GDG used a cost-effectiveness threshold of £20,000 per QALY to assess cost-effectiveness, which is the lower boundary of the cost-effectiveness threshold used by NICE.

analysis showed that small changes to the underlying assumptions (specifically) regarding the probability and duration of treatment-related adverse effects, dramatically altered the incremental cost-effectiveness ratio. Thus, the results from the analysis were not considered to be robust. It is anticipated that evidence from the ongoing MAPS trial (https://www.charttrials. abdn.ac.uk/maps/faq.php) and ProtecT trial (http://www.hta.nhsweb.nhs.uk/project/1230.asp) will contribute significantly to any update of this model, as both are collecting adverse event data associated with treatment options for men with localised prostate cancer, including radical prostatectomy.

In the absence of RCT data, threshold analysis was undertaken to assess how effective other treatments (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to be in order to be considered cost-effective. The analysis showed that relatively modest increases in QALYs were needed to be cost-effectiveness at a £30,000 per additional QALY level, thus while there is no direct evidence to support the cost-effectiveness of these treatments, the scope for them to be cost-effective is arguably large. It is also conceivable that if they are associated with fewer adverse events compared to watchful waiting/radical prostatectomy, yet do not confer better outcomes in terms of progression of the underlying prostate cancer, there is still potential for them to be cost-effective.

4.4.4 Radical prostatectomy

Clinical question: Which is the most effective radical prostatectomy method for prostate cancer: retropubic, transperineal, laparoscopic or robot-assisted laparoscopic radical prostatectomy?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all outcomes is summarised in Tables 24 - 26. A Health Technology Assessment (HTA) (Ramsey *et al*. 2012) was identified and results combined with relevant studies published since.

Overall survival

One study provided very low quality evidence of no deaths following either open (OP) or laparoscopic (LP) (time of follow-up not reported). Three very low quality studies reported the prevalence of death following OP and robot-assisted laparoscopic prostatectomy (RALP) at varying time points with conflicting results (follow-up ranging from 30 days to 1.5 years). Four very low quality studies found no deaths following either LP or RALP (follow-up 3-12 months where reported).

Biochemical disease-free survival

Ten studies provided very low quality evidence of PSA recurrence following LP compared with OP with varying results over a wide range of follow-up durations. Three of these provided comparable data which could be combined in a meta-analysis, which found no significant difference in risk of biochemical recurrence at 12 months following LP compared to OP (p=0.70).

Nine studies provided very low quality evidence of PSA recurrence following RALP compared with OP, again varying in length of follow-up and findings. Three of these provided data suitable for inclusion in a meta-analysis, which found a borderline significantly lower rate of biochemical recurrence at 12 months following RALP. The RR of 0.70 (95% CI 0.50-0.99)

Update 2014

suggests that for every 100 patients undergoing prostatectomy, three fewer would experience biochemical recurrence at 12 months if a RALP technique was used.

One very low quality study found no significant difference in PSA recurrence between LP and RALP groups at 3 months (Wolanski *et al*. 2012). One low quality study found no significant difference at 5 years (Magheli *et al*. 2011) and one at a mean of 4.1 years (Drouin *et al*. 2009). Six studies of very low quality were included in a network meta-analysis in 2010 (Ramsey *et al*. 2012) but no evidence of a difference between the two techniques was found. No new studies have been published reporting this information since 2010.

Treatment-related morbidity (transfusion rate)

Eighteen studies provided low quality evidence of a significantly lower rate of blood transfusion in patients undergoing LP compared to OP. Seventeen studies provided data in a format which could be included in a meta-analysis, this found an relative risk (RR) of 0.29 (95% CI 0.19-0.45) suggests that for every 100 patients undergoing prostatectomy, 41 fewer would need a blood transfusion if a laparoscopic technique was used.

Thirteen studies provided low quality evidence of a significantly lower rate of the blood transfusion during and following RALP compared with OP. The RR of 0.29 (95% CI 0.19-0.43) suggests that for every 100 patients undergoing prostatectomy, 11 fewer would need a blood transfusion if a RALP technique was used.

Ten studies provided very low quality evidence of blood transfusion rates in patients undergoing RALP compared with LP; findings varied across the studies. Nine of the studies provided suitable data for a standard meta-analysis, this found no significant difference in blood transfusion rates between RALP and LP (p=0.52). Thirty studies of very low quality were included in a network meta-analysis in 2010 but no evidence of a difference between the two techniques was found (Ramsey *et al*. 2012). Following restriction of the network meta-analysis to studies at low risk of bias there remained no significant difference. None of the four studies published since 2010 have found a significant difference in blood transfusion rates.

Update 2014

Adverse events (incontinence, erectile dysfunction)

A variety of different definitions and timescales for incontinence and erectile dysfunction were used in the studies, making comparisons difficult. Eleven studies compared incontinence following LP to OP; results were inconsistent. Four studies of very low quality provided data which could be included in a meta-analysis, which found no significant difference in incontinence rates between LP and OP at 6 months (p=0.27). Five studies of very low quality were included in a meta-analysis which found no significant difference in incontinence rates between LP and OP at 12 months (p=0.32). Eight studies compared erectile dysfunction following LP to OP; results were inconsistent. Two studies of very low quality were included in a meta-analysis and found a significantly lower rate following LP compared to OP at 6 months. The RR of 0.74 (95% CI 0.58-0.94) suggests that for every 100 patients undergoing OP, 17 less would experience erectile dysfunction if they had undergone LP. Five studies of very low quality were included in a meta-analysis which found no significant difference in incontinence rates between LP and OP at 12 months (p = 0.63).

Seven studies compared incontinence following RALP to OP; results were inconsistent. Two studies of low quality reported incontinence at 6 months following prostatectomy; one of which found a significantly lower rate following RALP compared to OP. Five studies of very low quality provided data which could be included in a meta-analysis, which found no significant difference in incontinence rates between RALP and OP at 12 months (p=0.08). Seven studies compared erectile dysfunction following RALP to OP; results were inconsistent. Four studies of very low quality were included in a meta-analysis and found a significantly lower rate following RALP compared to OP at 12 months. The RR of 0.61 (95%

CI 0.41-0.91) suggests that for every 100 patients undergoing OP, 15 fewer would experience erectile dysfunction if they had undergone RALP.

Eight studies of very low quality compared incontinence following RALP to LP. Two of the studies provided data which could be included in a meta-analysis, which found no significant difference in incontinence rates following RALP compared to LP at 12 months (p=0.31). Ten studies of very low quality were included in a network meta-analysis in 2010 but no evidence of a difference between the two techniques at 12 months was found (Ramsey *et al*. 2012). Neither of the two studies published since then found a significant difference in incontinence at 12 months. Five studies of very low quality compared erectile dysfunction following RALP to LP. One study found higher rates of erectile dysfunction at 3 months following RALP compared to LP (Joseph *et al*. 2005), one found higher rates following LP (Fiori *et al*. 2012), and two studies reported similar rates (Wolanski *et al*. 2012; Stolzenburg *et al*. 2013). Another study found higher rates of erectile dysfunction at 12 months following LP compared to RALP (Asimakopoulos *et al*. 2011).

Health-related quality of life

A variety of different tools and timescales for health-related quality of life were used in the studies, making comparisons difficult. Nine studies compared quality of life between patients undergoing LP and OP; results were inconsistent. Two studies of very low quality using the UCLA-PCI could be combined in a meta-analysis and found no significant difference in urinary function, urinary bother, sexual function, or sexual bother at 6 or 12 months. Two studies of very low quality using the SF-36 were included in a meta-analysis and found no significant difference in physical function, role limitation, bodily pain, mental health, or general health perception at 6 or 12 months.

Four very low quality studies compared quality of life between patients undergoing RALP or OP. One study (Mirza *et al*. 2011) found no significant difference in scores following either open retropubic or perineal prostatectomy compared to RALP in urinary, bowel, hormonal, sexual summary, or sexual function using the EPIC. Another study (Tewari *et al*. 2003) found VAS-assessed post-operative pain to be significantly higher on the day following OP than following RALP (p<0.05). A third study (Ball *et al*. 2006) found no significant difference in the proportion of patients meeting their baseline scores in urinary function, urinary bother, sexual function, or sexual bother at 6 months. While another study (Malcom *et al*. 2010) used the UCLA-PCI and found minimal differences in urinary function, urinary bother, sexual function, and sexual bother scores during 36 months of follow-up.

Four studies provided low quality evidence of a difference in quality of life between patients undergoing RALP and LP. Miller *et al*. (2007) found a significant difference in the physical component of the SF-12 between the two groups at 6 weeks (MD 3.6 95% CI 2.6-4.6) but not the mental component. Ball *et al*. (2006) found a significant difference in the proportion of patients reaching their baseline score of sexual function at 6 months in favour of RALP using the UCLA-PCI, but not in those reaching the baseline score of sexual bother, urinary function, or urinary bother. While Berge *et al*. (2013) also used to UCLA-PCI and found no significant difference in urinary function change from baseline between RALP and LP at 12 or 36 months, or in sexual function at 12 months. Willis *et al*. (2012) found no significant difference in the urinary function summary score or urinary function, urinary bother, sexual function, or sexual bother subscales of the EPIC between RALP and LP at 12 months. However, there was a borderline significant difference in the urinary irritative/obstructive subscale at 12 months (MD -3.1 95% CI -5.9 to -0.3) in favour of LP.

Operating time

Twenty-one studies provided very low quality evidence of a significantly longer operating time for LP compared to OP. Nineteen of the studies provided data which could be included

Update 2014

in a meta-analysis, which reported a significant mean difference of 73 minutes (95% CI 55-91) between the two techniques, in favour of LP (p<0.001).

Twelve studies provided very low quality evidence of a difference in operating time between RALP and OP; findings were inconsistent. All of the studies were included in a meta-analysis which reported no significant difference in operating time between the two techniques (p = 0.06).

Fifteen studies provided very low quality evidence of a difference in operating time between RALP and LP; findings were inconsistent. Fourteen of the studies provided data which could be included in a standard meta-analysis, which reported no significant difference in operating time between the two techniques (p=0.16). Eight directly comparative studies of very low quality were included in a network meta-analysis in 2010 and found a significant reduction of 12 minutes (95% CI 17-8) when undertaking RALP compared to LP (Ramsey *et al*. 2012). Of the studies published since 2010, one showed a significantly shorter time for RALP than LP, one a significantly shorter time for LP, and the four other studies showed no significant difference in operating time. However, results should be treated with caution due to uncertainty in whether robot docking time before commencing surgery was included in the measured operation time in all studies.

In-patient hospital stay

Eighteen studies provided very low quality evidence of a significant reduction in-patient hospital stay for LP compared to OP, with a mean difference of 1.4 days less (95% CI -1.7 to -1.0).

Eleven studies provided very low quality evidence of a longer in-patient stay following OP compared to RALP in all but one study. Two of the studies provided data which could be combined n a meta-analysis, which reported no significant difference in hospital stay between the two techniques (p=0.07).

Seven studies provided very low quality evidence of length of in-patient stay following RALP and LP; results were inconsistent. Three of the studies were included in a standard meta-analysis which reported no significant difference between the two techniques (p=0.32).

Positive margins

Twenty-six studies provided very low quality evidence of the proportion of patients with positive surgical margins following LP and OP; results were inconsistent. Twenty-four of the studies provided data which could be included in a meta-analysis, which reported a borderline significant difference in the rate of positive margins between the two techniques. The OR of 0.89 (95% CI 0.77-1.04) suggests that for every 100 patients two fewer will have positive surgical margins following LP compared to OP.

Twenty-one studies provided very low quality evidence of the proportion of patients with positive surgical margins following RALP and OP; results were inconsistent. All of the studies were included in a meta-analysis which reported no significant difference in the rate of positive margins between the two techniques (p=0.41).

Seventeen studies provided very low quality evidence of the proportion of patients with positive surgical margins following RALP and LP; results were inconsistent. All of the studies were included in a standard meta-analysis which reported no significant difference in the rate of positive margins between the two techniques (p=0.96). Thirty-seven very low quality studies were included in a network meta-analysis in 2010 and found a significant OR of 0.69 (95% CI 0.51-0.96), suggesting that for every 100 patients six fewer will have positive surgical margins following RALP compared to LP (Ramsey *et al*. 2012). Of the 11 studies published since 2010, ten (91%) found no significant difference in positive margin rates

Update 2014

between RALP and LP. However, these results should be treated with caution as none of the studies reported the same methodology for ascertainment of positive margin status.

Thirty-four very low quality studies provided information on the number of procedures carried out by participating surgeons. No evidence was found of a trend in the proportion of positive surgical margins with increasing surgeon experience for either LP or RALP (regression modeling; R2<0.02%) (Ramsey *et al*. 2012). There was no evidence that learning contributed differently to positive margin rates between the two procedures (p=0.76).

Update 2014

Disease-free survival and treatment-related mortality

These outcomes were not reported by any of the included studies.

Table 24: GRADE profile: what is the most effective radical prostatectomy method for prostate cancer? Comparison of laparoscopic (LP) and open (including retropubic and transperineal) (OP) methods

Quality assessment							Number of events		Effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirect-ness	Impreci-sion	Other considerations	LP	OP	Relative risk	95% CI	Absolute	Quality
Overall survival (follow-up not reported)												
1 (0)	Observational	None	None	None	Serious[1]	None	-	-	-	-	-	VERY LOW
Disease-free survival												
0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Biochemical recurrence (follow-up: 12 months)												
10 (3)	Observational	None	Serious[2]	None	None	None	35 / 323 (10.8%)	23 / 173 (13.3%)	RR 0.87	(0.44 – 1.74)	17 fewer per 1,000 (from 74 fewer to 98 more)	VERY LOW
Transfusion rate (follow-up: 10-65 months)												
18 (17)	Observational & 1 RCT	None	None	None	None	None	894 / 3324 (26.9%)	1748 / 3043 (57.4%)	RR 0.29	(0.19 – 0.45)	408 fewer per 1,000 (from 316 fewer to 365 fewer)	LOW
Treatment-related mortality												
0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Adverse events: incontinence (follow-up: 6 months)												
5 (4)	Observational	None	Serious[2]	None	Serious[3]	None	96 / 256 (37.5%)	64 / 249 (25.7%)	RR 1.44	(0.78 – 2.67)	113 more per 1,000 (from 57 fewer to 429 more)	VERY LOW

Quality assessment							Number of events		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirect-ness	Impreci-sion	Other considerations	LP	OP	Relative risk	95% CI	Absolute	
Adverse events: incontinence (follow-up: 12 months)												
8 (5)	Observational	Serious[4]	Serious[2]	None	Serious[5]	None	27 / 372 (7.3%)	50 / 463 (10.8%)	RR 0.76	(0.43 – 1.35)	26 fewer per 1,000 (from 62 fewer to 38 more)	VERY LOW
Adverse events: erectile dysfunction* (follow-up: 6 months)												
2 (2)	Observational	None	None	None	Serious[6]	None	53 / 108 (49.1%)	61 / 92 (66.3%)	RR 0.74	(0.58 – 0.94)	172 fewer per 1,000 (from 40 fewer to 278 fewer)	VERY LOW
Adverse events: erectile dysfunction* (follow-up: 12 months)												
7 (5)	Observational	Serious[7]	Serious[2]	None	None	None	224 / 370 (60.5%)	193 / 347 (55.6%)	RR 1.06	(0.85 – 1.32)	33 more per 1,000 (from 83 fewer to 178 more)	VERY LOW
Health-related quality of life – UCLA-PCI (follow-up: 1-12 months)												
4 (2)	Observational	Serious[8]	Serious[2]	None	None	None	-	-	-	-	-	VERY LOW
Health-related quality of life – SF-36 (follow-up: 1-12 months)												
2 (2)	Observational	Serious[9]	Serious[2]	None	None	None	-	-	-	-	-	VERY LOW
Operating time (follow-up: NA)												
21 (19)	Observational & 1 RCT	Serious[10]	None	None	None	None	-	-	MD 73	(55 – 91)	73 minutes more (from 55 more to 91 more)	VERY LOW

Quality assessment							Number of events		Effect			Quality
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirect-ness**	**Impreci-sion**	**Other considerations**	**LP**	**OP**	**Relative risk**	**95% CI**	**Absolute**	
In-patient stay (follow-up: 6-65 months)												
18 (18)	Observational	Serious[11]	None	None	None	None	-	-	MD -1.4	(-1.7 – -1.0)	1.4 days less (from 1.7 less to 1.0 less)	VERY LOW
Positive surgical margins (follow-up: 6-65 months)**												
26 (24)	Observational & 1 RCT	Serious[12]	None	None	None	None	1053 / 4889 (21.5%)	2401 / 9222 (26.0%)	RR 0.89	(0.77 – 1.04)	22 fewer per 1,000 (from 47 fewer to 8 more)	VERY LOW

Some studies referred to potency instead of erectile dysfunction; definitions of the two terms varied (see Table 89 in the Evidence Review).

***A positive surgical margin is the area around the edge of the prostate following surgical removal which is positive for prostate cancer cells and reflects the likelihood of cancerous cells remaining behind in the prostate bed. It may therefore impact prognosis and the need for adjuvant therapy after surgery.*

1 No events occurred in either group and total number of patients was less than 300. 2 Study results varied considerably. 3 Wide confidence intervals and number of events < 300.

4 Four (50%) studies were reported to be at high risk of bias by the HTA. 5 Number of events was less than 300. 6 Number of events < 300 & total number of patients < 300.

7 Three (43%) studies were reported to be at high risk of bias by the HTA; risk of bias was not reported for one (14%) study. 8 Two (50%) studies were reported to be at high risk of bias by the HTA.

9 One (50%) study was reported to be at high risk of bias by the HTA. The risk of bias was not reported for one (50%) study. 10 Four (21%) studies were reported to be at high risk of bias by the HTA; 4 (21%) were reported to be at unclear risk of bias; and risk of bias was not reported for 5 (26%).

11 Three (17%) studies were reported to be at high risk of bias by the HTA; five (28%) were reported to be of unclear risk of bias; and risk of bias was not reported for six (33%).

12 Six (23%) studies were reported to be at high risk of bias by the HTA; four (15%) were of unclear risk of bias; and risk of bias was not reported for 5 (31%).

Table 25: GRADE profile: what is the most effective radical prostatectomy method for prostate cancer? Comparison of robot-assisted laparoscopic (RALP) and open (including retropubic and transperineal) (OP) methods 2

Quality assessment							Number of events		Effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other considerations	RALP	OP	Relative risk	95% CI	Absolute	Quality
Overall survival (follow-up: 8-30 months)												
3 (0)	Observational	Serious[1]	Serious[2]	None	Serious[3]	None	-	-	-	-	-	VERY LOW
Disease-free survival												
0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Biochemical recurrence (follow-up: 12 months)												
9 (3)	Observational	Serious[4]	None	None	Serious[5]	None	46 / 640 (7.2%)	91 / 957 (9.5%)	RR 0.70	(0.50 – 0.99)	29 fewer per 1,000 (from 1 fewer to 48 fewer)	VERY LOW
Transfusion rate (follow-up: 8-58 months)												
13 (13)	Observational	Serious[6]	None	None	None	Strong association[7]	139 / 4077 (3.4%)	452 / 3055 (14.8%)	RR 0.29	(0.19 – 0.43)	105 fewer per 1,000 (from 84 fewer to 120 fewer)	LOW
Treatment-related mortality												
0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Adverse events: incontinence (follow-up: 12 months)												
6 (5)	Observational	Serious[8]	Serious[2]	None	Serious[9]	None	11 / 256 (4.3%)	44 / 398 (11.1%)	RR 0.43	(0.16 – 1.15)	63 fewer per 1,000 (from 93 fewer to 17 more)	VERY LOW
Adverse events: erectile dysfunction (follow-up: 12 months)												
4 (4)	Observational	Serious[10]	None	None	Serious[11]	Strong association[7]	89 / 305 (29.2%)	181 / 464 (39.0%)	RR 0.61	(0.41 – 0.91)	152 fewer per 1,000 (from 35 fewer to 230 fewer)	VERY LOW

Quality assessment							Number of events		Effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirect-ness**	**Imprecision**	**Other considerations**	**RALP**	**OP**	**Relative risk**	**95% CI**	**Absolute**	**Quality**
Health-related quality of life (follow-up: 0-18 months)												
4 (0)	Observational	Serious[12]	None	None	None	None	-	-	-	-	-	VERY LOW
Operating time (follow-up: 11-58 months)												
12 (12)	Observational	Serious[13]	Serious[2]	None	None	None	-	-	MD 25	(-1 – 50)	25 minutes more (from 1 less to 50 more)	VERY LOW
In-patient stay (follow-up: 11-24 months)												
11 (2)	Observational	Serious[14]	None	None	Serious[15]	None	-	-	MD -1.8	(-3.8 – 0.1)	1.8 days less (from 3.8 less to 0.1 more)	VERY LOW
Positive surgical margins (follow-up: 8-58 months)												
21 (21)	Observational	Serious[16]	Serious[2]	None	None	None	1172 / 6136 (19.1%)	1384 / 7418 (18.7%)	RR 0.94	(0.80 – 1.10)	11 fewer per 1,000 (from 37 fewer to 19 more)	VERY LOW

1 *1 All three (100%) studies were reported to be at high risk of bias by the HTA. 2 Variation in study results. 3 Total number of events is less than 100.*
2 *4 Five (63%) studies were reported to be at high risk of bias by the HTA. 5 Less than 300 events in total.*
3 *6 Eight (67%) studies were reported to be at high risk of bias by the HTA; one (13%) was of unclear risk; and risk of bias was not reported for one (13%) study.*
4 *7 OR < 0.5. 8 Four (80%) studies were reported to be at high risk of bias by the HTA; one (20%) study was of unclear risk of bias.*
5 *9 Total number of events is less than 300; wide confidence intervals.*
6 *10 All four (100%) studies were reported to be at high risk of bias by the HTA. 11 Less than 300 events and wide confidence intervals.*
7 *12 One (25%) study was reported to be at high risk of bias by the HTA; risk of bias was not reported for one (25%) study.*
8 *13 Six (50%) studies were reported to be at high risk of bias by the HTA; two (17%) were reported to be at unclear risk of bias.*
9 *14 Six (55%) studies were reported to be at high risk of bias by the HTA; two (18%) were of unclear risk of bias; and risk of bias was not reported for two (18%) studies.*
10 *15 Total number of patients included in meta-analysis is less than 100.*
11 *16 Eight (44%) studies were reported to be at high risk of bias by the HTA; two (11%) studies were of unclear risk of bias; and risk of bias was not reported for one (6%)*
12 *study.*

Table 26: GRADE profile: what is the most effective radical prostatectomy method for prostate cancer? Comparison of robot-assisted laparoscopic (RALP) and laparoscopic (LP) methods 2

Quality assessment							Number of events		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other considerations	RALP	LP	Relative risk	95% CI	Absolute	
Overall survival (follow-up: 2-12 months)												
4 (0)	Observational & 1 RCT	Serious[1]	None	None	Serious[2]	None	-	-	-	-	-	VERY LOW
Disease-free survival												
0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Biochemical recurrence (follow-up: 4-36 months)												
0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
6*	Observational	Serious[3]	None	None	Serious[4]	None	49 / 640 (7.7%)	35 / 323 (10.8%)	RR 0.89	(0.24 – 3.34)	11 fewer per 1,000 (from 80 fewer to 180 more)	VERY LOW
Transfusion rate (follow-up:2-65 months)												
10 (9)	Observational & 2 RCTs	Serious[5]	Serious[6]	None	Serious[4]	None	48 / 1829 (2.6%)	69 / 1899 (3.6%)	RR 0.79	(0.39 – 1.61)	8 fewer per 1,000 (from 22 fewer to 22 more)	VERY LOW
30*	Observational & 1 RCT	Serious[7]	None	None	Serious[8]	None	(3.5%)	(5.0%)	RR 0.71	(0.31 – 1.62)	15 fewer per 1,000 (from 37 fewer to 31 more)	VERY LOW
Treatment-related mortality												
0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Adverse events: incontinence (follow-up: 12 months)												
8 (2)	Observational & 2 RCTs	None	None	None	Serious[4]	None	14 / 96 (14.6%)	42 / 176 (23.9%)	RR 0.65	(0.26 – 1.62)	84 fewer per 1,000 (from 177 fewer to 148 more)	VERY LOW

Quality assessment							Number of events		Effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirect-ness**	**Imprecision**	**Other considerations**	**RALP**	**LP**	**Relative risk**	**95% CI**	**Absolute**	**Quality**
10*	Observational	Serious[9]	Serious[6]	None	Serious[4]	None	(4.5%)	(7.9%)	RR 0.55	(0.09 – 2.84)	54 fewer per 1,000 (from 116 fewer to 168 more)	VERY LOW
Adverse events: erectile dysfunction (follow-up: 12 months)												
5 (0)	Observational & 2 RCTs	None	None	None	Serious[10]	None	-	-	-	-	-	VERY LOW
Health-related quality of life (follow-up: 1-12 months)												
4 (0)	Observational	None	None	None	None	None	-	-	-	-	-	LOW
Operating time (follow-up: 2-58 months)												
15 (14)	Observational & 2 RCTs	Serious[11]	Serious[6]	None	Serious[8]	None	-	-	MD -12	(-29 – 4)	12 minutes less (from 29 less to 4 more)	VERY LOW
8*	Observational	Serious[12]	Serious[6]	None	None	None	-	-	MD -12	(-17 – -8)	12 minutes less (from 17 less to 8 less)	VERY LOW
In-patient stay (follow-up: 3-36 months)												
7 (3)	Observational	Serious[13]	None	None	None	None	-	-	MD -0.40	(-1.18 – 0.39)	0.4 days less (from 1.2 less to 0.4 more)	VERY LOW
Positive surgical margins (follow-up: 2-65 months)												
17 (17)	Observational & 3 RCTs	Serious[14]	Serious[6]	None	Serious[8]	None	405 / 2530 (16.0%)	514 / 2667 (19.3%)	RR 1.02	(0.73 – 1.40)	4 more per 1,000 (from 52 fewer to 77 more)	VERY LOW

Quality assessment							Number of events		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other considerations	RALP	LP	Relative risk	95% CI	Absolute	
37*	Observational & 1 RCT	Serious[15]	Serious[6]	None	None	None	17.6%	23.6%	RR 0.69	(0.51 – 0.96)	62 fewer per 1,000 (from 8 fewer to 104 fewer)	VERY LOW

**Results of a mixed treatment comparison model conducted by a Health Technology Assessment in 2010.*
1 Three (75%) studies were reported by the HTA to be at high risk of bias. 2 Less than 300 events in total.
3 Three studies (50%) were judged by the HTA to be at high risk of bias; two studies (33%) at unclear risk of bias; and one study (17%) was at low risk of bias. 4 Less than 300 events in total and wide confidence intervals reported.
5 Three (33%) studies reported by HTA to be at high risk of bias. 6 Inconsistency in results of studies included.
7 The HTA reports high risk of bias in 10 (33%) studies; low risk in 8 (27%); risk is reported as unclear in 7 (23%). Risk of bias is not reported for 5 (17%) studies.
8 Wide confidence intervals reported.
9 Six (60%) of the studies were reported to be at high risk of bias by the HTA; 2 (20%) were low risk; one (10%) was of unclear risk; and risk was not reported for one (10%).
10 Less than 100 events and less than 300 participants.
11 Three (25%) studies were reported by the HTA to be at high risk of bias; one (8%) was at low risk; and risk of bias was not reported for four (33%) studies.
12 Three (38%) studies were reported by the HTA to be at high risk of bias; one (13%) was at low risk; and risk of bias was not reported for four (50%) studies.
13 One study (17%) is reported to be at high risk of bias by the HTA; risk of bias is not reported for three (50%) studies.
14 Three (23%) studies were reported by the HTA to be at high risk of bias; eight (62%) were at low risk; and risk was not reported for two (15%) studies.
15 Seventeen (46%) studies were reported to be at high risk of bias by the HTA; 8 (22%) were at low risk; risk was unclear in 6 (16%); and risk of bias was not reported in 6 (16%).

Cost-effectiveness evidence (see also full evidence review) (2014)

A literature review of published economic evidence identified two relevant papers; Hohwu *et al*. 2011 and Ramsay *et al*. 2012. Ramsay *et al*. 2012 was a comprehensive report conducted as part of the NIHR HTA programme. Both papers were cost-utility analyses that quantified health effects in terms of quality adjusted life years (QALYs). The primary results of the analyses by Hohwu *et al*. 2011 and Ramsay *et al*. 2012 are summarised in the modified Table 27.

Despite the high economic importance of this topic, no further health economic analysis was undertaken. This is because the economic analysis conducted in this study was deemed to be of sufficiently high equality to be used by the GDG when making their recommendations.

Study quality and results

Hohwu *et al* was deemed only partially applicable to the guideline, primarily because it considered a country other than the UK (Denmark). Ramsay *et al*. 2012, on the other hand, was deemed to be directly applicable because it considered a UK setting and there were no other applicability issues.

Potentially serious limitations were identified in the study by Hohwu *et al*. The one year time horizon was possibly too short to capture all the relevant costs and benefits (as a comparison, Ramsay *et al*. 2012 considered a ten year time horizon). Also, while numerous one-way sensitivity analyses were conducted, additional analyses could have been conducted in other important areas. No serious limitations were identified with Ramsay *et al*. 2012. However, there were a few minor limitations with some important information not being reported (e.g. price year) and an important (and uncertain) parameter left out of the probabilistic sensitivity analysis (PSA).

Evidence statements

The conclusions of in the two studies were markedly different. Hohwu *et al*. 2011 found robot assisted laparoscopic prostatectomy (RALP) to be dominated by radical retropubic prostatectomy (RRP) i.e. RRP was both more effective and less costly. Conversely, Ramsay *et al*. found robot assisted prostatectomy to be cost-effective in at least some scenarios when compared to laparoscopic prostatectomy. Given the better applicability and fewer limitations associated with Ramsay *et al*. 2012, more weight is attached their results.

The results of the sensitivity analysis in Ramsay *et al*. suggest that the cost-effectiveness of robot assisted prostatectomy is highly dependent upon the number of procedures conducted per year (thereby affecting the cost per procedure) and the positive margin rates.

Update 2014

Table 27: Modified GRADE table showing the included evidence (Hohwu *et al*. 2011 and Ramsay *et al*. 2012) comparing methods of radical prostatectomy

Study	Population	Comparators	Costs	Effects	Incremental costs	Incremental effects	ICER	Uncertainty	Applicability and limitations
Hohwu *et al*. 2011	Men with clinically localised prostate cancer who underwent radical prostatectomy .	Retropubic radical prostatectomy (RRP)	€3,863 (direct costs only) €12,465 (incl. Indirect costs)	27% successful operation 0.0116 QALYs	Reference			One-way sensitivity analysis was conducted on numerous variables. The ICERs ranged from €20,000 TO €150,000 per QALY. Probabilistic sensitivity analysis was not required as the analysis was not based on a model.	Partially applicable Not a UK study (Denmark). Potentially serious limitations Many inputs were not sourced through systematic review. Time horizon may be too short to capture all outcomes. Further sensitivity analyses could have
		Robot assisted laparoscopic prostatectomy (RALP)	€8,369 (direct costs only) €13,411 (incl. Indirect costs)	34% successful operation 0.0103 QALYs	€4,506 (direct costs only) €946 (incl. indirect costs)	7% successful operation -0.0013 QALYs	€64,343 per successful operation (direct costs) €13,514 per successful operation (indirect costs) RRP is dominant when considering QALYs		

Study	Population	Comparators	Costs	Effects	Incremental costs	Incremental effects	ICER	Uncertainty	Applicability and limitations
									been conducted.
Ramsay *et al*. 2012 (NIHR HTA on radical prostatectomy)	Men with localised prostate cancer requiring radical prostatectomy.	Laparoscopic prostatectomy	£7,628	6.44 QALYs	Reference			Numerous one-way sensitivity analyses were conducted. As in the base case, results were presented according to throughput and robotic systems. ICERs ranged from £1,436 to £50,502 per QALY with robotic surgical capacity = 200. A two-way sensitivity analysis was also conducted whereby two of the most influential variables (cost per procedure	Directly applicable Minor limitations
		Robot assisted prostatectomy (Numerous surgical capacity scenarios were considered).	Capacity = 200: £9,040 Capacity = 150: £9,799 Capacity = 100: £11,312 Capacity = 50: £15,859 Capacity = 200 with cheaper equipment cost: £8,186	6.52 QALYs	Capacity = 200: £1,412 Capacity = 150: £2,171 Capacity = 100: £3,684 Capacity = 50: £8,231 Capacity = 200 with cheaper equipment cost: £540	0.08 QALYs	Capacity = 200: £18,329 Capacity = 150: £28,172 Capacity = 100: £47,822 Capacity = 50: £106,839 Capacity = 200 with cheaper equipment cost: £7,009		

Study	Population	Comparators	Costs	Effects	Incremental costs	Incremental effects	ICER	Uncertainty	Applicability and limitations
								and positive margin rates) were altered simultaneously. The results of this analysis were presented graphically. Probabilistic sensitivity analysis was also conducted. Robotic surgery was found to have a 95% probability of being cost-effective with robotic surgical capacity = 200.	

Update 2014

1

Recommendations	**Commissioners of urology services should consider providing robotic surgery to treat localised prostate cancer. [new 2014]** **Commissioners should ensure that robotic systems for the surgical treatment of localised prostate cancer are based in centres that perform at least 150 radical prostatectomies per year. [new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of margin status, transfusion rate, length of stay and adverse events to be the most important as they showed clinically important differences between robotic, laparoscopic and open prostatectomy techniques. Disease-free survival and treatment-related mortality were not reported in the evidence.
Quality of the evidence	There was very low quality clinical evidence for margin status and length of stay; very low to moderate quality evidence for transfusion rate and very low to low quality evidence for adverse events. The GDG noted the following limitations with the clinical evidence: The data were mostly observational and all grouped together rather than separated according to stage The patient population may have been different in different studies Differences in the care pathways in non-UK healthcare settings could influence some of the outcomes measured – for example length of hospital stay. The GDG also noted that the economic evidence came from a published cost-utility analysis. This evidence was assessed as directly applicable with minor limitations but the GDG agreed there was uncertainty around the key clinical input data used. Consequently there was also uncertainty about the conclusions of the economic evidence.
Trade-off between clinical benefits and harms	The GDG considered that robotic surgery was likely to result in less transfusions and a shorter hospital stay compared with other types of surgery. However there could potentially be a need for increased travel as the robots are not available at every centre. It was agreed that the potential benefits outweighed the potential harms. The GDG noted that the HTA had shown there were significantly less positive surgical margins with robot-assisted prostatectomy compared to laparoscopic prostatectomy. Whilst studies published since the HTA had found no significant difference in positive margin rates between robot-assisted prostatectomy compared to laparoscopic prostatectomy, the GDG noted that this was based on a limited number of studies which had not used the same methodology for ascertainment of positive margin rates. They therefore agreed to put more weight on the results of the HTA. Due to the uncertainty in the evidence the GDG agreed it was only possible for them to recommend that provision of robotic surgery be considered.
Trade-off between net health benefits and resource use	The GDG noted that the results of the published cost-utility analysis had shown that robotic surgery was cost effective with an ICER of £28,172/QALY. However this was dependent on a minimum of 150 procedures being performed. Therefore the GDG recommended that robotic systems should be based in centres where the caseload is greater than 150 cases per year.
Other	The GDG noted that currently there is not enough capacity (either in terms of number of robots or people trained to use them) for all prostatectomies to be performed robotically. They therefore agreed not to recommend that laparoscopic or open prostatectomy no longer be performed, so that these

Update 2014

	could continue to be alternative treatment options and help alleviate any capacity issues.

Update 2014

4.4.15 Radical radiotherapy

Radiotherapy can be delivered to the prostate in two ways; either using external x-ray beams from a linear accelerator or by radiation sources placed directly into the prostate gland (brachytherapy). Radical external beam radiotherapy techniques have evolved to optimise the dose to the tumour while minimising the risks of normal tissue damage. Current examples of such techniques include image-guided radiotherapy (IGRT) and intensity-modulated radiotherapy (IMRT). There are two different radiation sources used in prostate cancer brachytherapy; low dose rate I125 seeds which are implanted and remain in the prostate lifelong (permanent implants) or high dose rate Ir192 delivered using an after loading machine directed into the prostate along implanted plastic tubes which are subsequently removed (temporary implant). Theoretically brachytherapy can deliver a higher dose than external beam radiotherapy as it does not traverse normal tissues to reach the prostate, however it may itself deliver higher doses to the urethra. Possible side effects include alteration in urinary and bowel function and erectile dysfunction (see section 4.5).

Recommendations	**Do not offer brachytherapy alone to men with high-risk localised prostate cancer. [2008]**
Qualifying statement	There is no strong evidence for the benefit of one treatment over another. Relatively little health gain is required for these interventions to become demonstrably cost-effective.
Recommendation	**For men with localised prostate cancer[j] receiving radical external beam radiotherapy with curative intent, offer planned treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage. [2008]**
Qualifying statement	There is evidence from randomised controlled trials that conformal radiotherapy reduces toxicity compared with conventional radiotherapy at similar dose.
Recommendation	**Offer men undergoing radical external beam radiotherapy for localised prostate cancer[q] a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction. [2008]**
Qualifying statement	There is evidence from randomised controlled trials to support making this recommendation.
Recommendation	**Offer androgen deprivation therapy in line with recommendation on page 256.**

Clinical evidence (2008)

Conformal vs. conventional radiotherapy

Three randomised trials were identified (Dearnaley *et al*. 1999; Koper *et al*. 2004; Pollack *et al*. 2002). Two were direct comparisons of conformal and conventional radiotherapy (Dearnaley *et al*. 1999; Koper *et al*. 2004) and the other examined conventional radiotherapy with or without an 8Gy conformal boost (Pollack *et al*. 2002). The evidence suggested reduced gastrointestinal and urinary toxicity with conformal radiotherapy. Follow-up was insufficient to compare overall survival. There was no evidence of a difference in biochemical failure rate in the trials that directly compared conformal with conventional radiotherapy (Dearnaley *et al*. 1999; Koper *et al*. 2004).

j This may also apply to some men with locally advanced prostate cancer

Radiotherapy dose

Randomised trials have examined dose escalation in conformal radiotherapy for prostate cancer (Peeters *et al*. 2006; Dearnaley *et al*. 2007; Dearnaley *et al*. 2005; Pollack *et al*. 2002), although Pollack *et al*. only used a conformal radiotherapy boost. There was consistent evidence of improved biochemical progression-free survival in the higher dose groups, at the cost of increased late bowel toxicity. Longer follow-up is needed before overall or disease specific survival can be compared.

Two randomised controlled trials (Lukka *et al*. 2005; Yeoh *et al*. 2003) have compared hypofractionated (fractions of 2.6Gy or more) with conventionally fractionated (2Gy fractions) radiotherapy in this population, but at doses lower than currently used. One trial (Lukka *et al*. 2005) reported overall survival, and found no significant difference between groups at a median follow-up of 5.7 years. There was no evidence about the effect of hypofractionation on disease specific survival, but the evidence suggests an increased risk of biochemical failure and acute treatment toxicity with hypofractionated radiotherapy.

Brachytherapy

There were no randomised trials comparing brachytherapy with other radical therapies or with watchful waiting. Systematic reviews of observational studies (Hummel *et al*. 2003; Doust *et al*. 2004; Norderhaug *et al*. 2003; Nilsson *et al*. 2004) found insufficient evidence to compare overall and disease specific survival after brachytherapy with that after other radical therapies. Evidence from these systematic reviews suggests that, at least for low-risk patients, biochemical recurrence free survival after brachytherapy is equivalent to that after external beam radiotherapy or prostatectomy. Evidence from systematic reviews comparing the toxicity of radical therapies for prostate cancer (Hummel *et al*. 2003; Doust *et al*. 2004; Nilsson *et al*. 2004) suggest brachytherapy has a similar adverse event rate to prostatectomy or external beam radiotherapy, but such comparisons are based on evidence from observational studies. Some reports of brachytherapy case series suggest lower rates of impotence and incontinence than seen with surgery or EBRT but higher rates of obstructive and irritative urinary symptoms.

4.4.6 Combined external beam radiotherapy and brachytherapy

Brachytherapy has become accepted as a standard of care for low-risk localised prostate cancer, but its role in high risk disease is less clear. External beam radiotherapy (in combination with hormone therapy) for patients with high risk prostate cancer is now standard treatment, and it is postulated that brachytherapy may also have a role to play in this group. However brachytherapy does not deliver significant radiation dose outside the prostate capsule which may be important particularly in high risk and locally advanced disease when extracapsular extension is more prevalent, hence a combination of the two approaches may be optimal.

Update 2014

Clinical question: Is the combination of brachytherapy with external beam radiotherapy more effective than either method alone for localised or locally advanced non metastatic prostate cancer?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all outcomes is summarised in Tables 28 - 31.

Overall survival

Moderate quality evidence suggests uncertainty about whether overall survival is equivalent or worse in men treated with external beam radiotherapy (EBRT) and high dose rate brachytherapy (HDR-BT) combined when compared to men treated with EBRT alone. The pooled hazard ratio from two randomised trials for all cause mortality (combined versus EBRT) was 1.44 (95% C.I. 0.87 to 2.40). Very low quality evidence from a meta-analysis of non-randomised studies (Pieters *et al*. 2009) suggests a survival benefit for combined EBRT and HDR-BT compared to EBRT alone (HR 0.67; 95% CI 0.58-0.78).

Biochemical disease-free survival

Moderate quality evidence suggests better biochemical failure-free survival when men are treated with EBRT and HDR-BT combined than when treated with EBRT alone (HR 0.57; 95% CI 0.41-0.79). However this evidence comes from randomised trials that used lower doses in their EBRT-only arms (66 Gy and 50 Gy respectively) than the minimum of 74 Gy recommended in the 2008 NICE prostate cancer guideline. Very low quality evidence from a meta-analysis of non randomised studies (Pieters *et al*. 2009) suggests better biochemical failure free survival combined EBRT and HDR-BT when compared to EBRT alone (HR 0.71; 95% CI 0.66-0.76).

A systematic review (Bannuru *et al*. 2011) identified a very low quality, small, observational study (Wong *et al*. 2009), which found no significant difference in biochemical failure-free survival of the two treatment arms at 5 years: 94% versus 87% for EBRT and low dose rate brachytherapy (LDR-BT) and EBRT respectively.

A systematic review (Bannuru *et al*. 2011) identified very low quality evidence of EBRT and LDR-BT versus LDR-BT alone from two small observational studies with conflicting results. Da Silva Franca *et al*. (2010) reported better biochemical failure free survival with combined therapy than with LDR-BT alone at 5 years whereas Wong *et al*. (2009) found no significant difference.

Update 2014

Low quality evidence suggests uncertainty about whether biochemical failure differs between higher and lower doses of supplemental EBRT. The evidence comes from a single randomised trial (Merrick *et al*. 2012) in which only 15 men experienced biochemical failure. The resulting confidence intervals (EBRT 40 Gy + LDR-BT versus EBRT 20 Gy + LDR-BT; HR 1.0; 95% CI 0.36-2.76) are wide enough to include the possibility that either treatment option could be superior to the other.

Treatment-related morbidity

There is low quality evidence of uncertainty about the relative rates of gastrointestinal (GI) complications in EBRT+ HDR-BT and EBRT (OR 1.48; 95% CI 0.55-4.01). Gastrointestinal complications were reported in 6% and 4% of men treated with EBRT+HDR-BT and EBRT respectively. There is also low quality evidence of uncertainty about the relative rates of genitourinary (GU) in EBRT+ HDR-BT and EBRT (OR 1.24; 95% CI 0.71-2.17). Genitourinary complications were reported in 22% and 19% of men treated with EBRT+HDR-BT and EBRT respectively.

Very low quality evidence from an observational study found late grade 3 GI and GU toxicity were more likely with EBRT+LDR-BT than with EBRT alone (Wong *et al*. 2009).

A systematic review (Bannuru *et al*. 2011) identified two relevant observational studies which provided uncertainty about the relative rates of late GI complications in EBRT+LDR-BT versus LDR-BT alone (OR 5.31 95% CI 0.73-38.74). For late GU complications there was similar uncertainty (OR 1.08 95% CI 0.49-2.4).

Health-related quality of life

Moderate quality evidence suggests equivalent health-related quality of life following combined EBRT+HDR-BT and EBRT alone. Hoskin *et al*. (2007) found average FACT-P scores returned to pre-treatment levels with 6 months of treatment in both the EBRT+HDR-BT and EBRT alone treatment groups. No significant differences in mean FACT scores were found for any of the three domains: general, prostate and Trial Outcome Index (TOI), or in erectile function scores over a 10.5 year follow-up period (Hoskin *et al*. 2013).

Update 2014

Disease-free survival and treatment-related mortality

These outcomes were not reported by any of the included studies.

Table 28: GRADE profile: is the combination of brachytherapy with external beam radiotherapy more effective than either method alone for localised or locally advance non-metastatic prostate cancer? Comparison: external beam radiotherapy (EBRT) + high dose rate brachytherapy (HDR-BT) versus EBRT alone

Quality assessment							Number of patients		Effect			
No of studies*	Design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other consid-erations	EBRT + HDR-BT	EBRT alone	Relative risk	95% CI	Absolute	Quality
Overall survival												
2	RCTs	None	None	None	Serious[1]	None	36/161 (22.4%)	26/159 (16.4%)	HR 1.44	(0.87 – 2.4)	Not reported	MODERATE
27	Observational	Very serious[2]	None	None	None	None	Not reported	Not reported	HR 0.67	(0.58 – 0.78)	Not reported	VERY LOW
Disease-free survival												
0	-	-	-	-	-	-	-	-	-	-	-	–
Biochemical disease-free survival												
2	RCTs	None	None	None	Serious[1]	None	59/160 (36.9%)	122/159 (76.7%)	HR 0.57	(0.41 – 0.79)	5 yr BF-free survival 71-75% for EBRT+HDRBT versus 39-61% for EBRT	MODERATE
27	Observational	Very serious[2]	None	None	None	None	Not reported	Not reported	HR 0.71	(0.66 – 0.76)	Not reported	VERY LOW
Treatment-related morbidity: late GI complications (grade 3 or more)												
2	RCTs	None	None	None	Very serious[1]	None	10/158 (6.3%)	7/161 (4.3%)	OR 1.48	(0.55 – 4.01)	20 more per 1000 (from 19 fewer to 111 more)	LOW
Treatment-related morbidity: late GU complications (grade 3 or more)												
2	RCTs	None	None	None	Very serious[1]	None	35/158 (22.2%)	30/161 (18.6%)	OR 1.24	(0.71 – 2.17)	35 more per 1000 (from 46 fewer to 146 more)	LOW
Health-related quality of life: 1 year post-treatment (measured using FACT-P)												

1	RCT	Serious	None	None	None	None	73	67	-	-	MD 0 (5.66 lower to 5.66 higher)	LOW

1 *[1] Low number of events. [2] Observational studies. Patient characteristics not well balanced between EBRT and EBRT+HDR-BT studies.*
2

Table 29: GRADE profile: is the combination of brachytherapy with external beam radiotherapy more effective than either method alone for localised or locally advance non-metastatic prostate cancer? Comparison: external beam radiotherapy (EBRT) + low dose rate brachytherapy (LDR-BT) versus EBRT alone

Quality assessment							Number of patients		Effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EBRT + HDR-BT	EBRT alone	Relative risk	95% CI	Absolute	Quality
Overall survival												
0	-	-	-	-	-	-	-	-	-	-	-	-
Disease-free survival												
0	-	-	-	-	-	-	-	-	-	-	-	-
Biochemical disease-free survival												
1	Observational	Very serious[2]	None	None	Serious[1]	None	44	314	Not reported	Not reported	94% EBRT+LDR-BT versus 87% EBRT at 5 years	VERY LOW
Treatment-related morbidity: GI complications												
1	Observational	Very serious[2]	None	None	Serious[1]	None	2 / 44 (4.5%)	3 / 314 (1.0%)	OR 4.94	(0.80 – 30.41)	36 more per 1,000 (from 2 fewer to 217 more)	VERY LOW
Treatment-related morbidity: GU complications												
1	Observational	Very serious[2]	None	None	Serious[1]	None	8 / 44 (18.2%)	16 / 314 (5.1%)	OR 4.41	(1.66 – 10.35)	140 more per 1,000 (from 31 more to 306 more)	VERY LOW
Treatment-related mortality												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life: 1 year post-treatment												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Low number of events. 2 Observational studies. Patient characteristics not well balanced between EBRT and EBRT+LDR-BT studies.

Table 30: GRADE profile: is the combination of brachytherapy with external beam radiotherapy more effective than either method alone for localised or locally advance non-metastatic prostate cancer? Comparison: external beam radiotherapy (EBRT) + low dose rate brachytherapy (LDR-BT) versus LDR-BT alone

Quality assessment							Number of patients		Effect			Quality
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EBRT + HDR-BT**	**EBRT alone**	**Relative risk**	**95% CI**	**Absolute**	
Overall survival												
0	-	-	-	-	-	-	-	-	-	-	-	-
Disease-free survival												
0	-	-	-	-	-	-	-	-	-	-	-	-
Biochemical disease-free survival												
2	Observational	Very serious[2]	Serious[3]	None	Serious[1]	None	68	297	Not reported	Not reported	94% EBRT+LDR-BT versus 54-94% LDR-BT at 5 years	VERY LOW
Treatment-related morbidity: GI complications												
2	Observational	Very serious[2]	None	None	Serious[1]	None	2 / 171 (1.2%)	2 / 351 (0.6%)	OR 5.31	(0.73 – 38.74)	24 more per 1,000 (from 2 fewer to 176 more)	VERY LOW
Treatment-related morbidity: GU complications												
2	Observational	Very serious[2]	None	None	Serious[1]	None	9 / 171 (5.3%)	41 / 351 (11.7%)	OR 1.08	(0.49 – 2.40)	8 more per 1,000 (from 56 fewer to 124 more)	VERY LOW
Treatment-related mortality												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life: 1 year post-treatment												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Low number of events. 2 Observational studies. Patient characteristics not well balanced between EBRT and EBRT+LDR-BT studies. 3 Large difference in 5 year biochemical failure free survival of the LDR-BT arms of the studies (54% versus 94%)

Table 31: GRADE profile: is the combination of brachytherapy with external beam radiotherapy more effective than either method alone for localised or locally advance non-metastatic prostate cancer? Comparison: external beam radiotherapy 40 Gy (EBRT-40Gy) + low dose rate brachytherapy (LDR-BT) versus EBRT-20Gy + LDR-BT

Quality assessment							Number of patients		Effect			Quality
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EBRT + HDR-BT**	**EBRT alone**	**Relative risk**	**95% CI**	**Absolute**	
Overall survival												
0	-	-	-	-	-	-	-	-	-	-	-	-
Disease-free survival												
0	-	-	-	-	-	-	-	-	-	-	-	-
Biochemical disease-free survival												
1	RCT	Serious[2]	None	None	Serious[1]	None	8 / 125 (6.4%)	7 / 122 (5.7%)	HR 1.00	(0.36 – 2.76)	Not reported	LOW
Treatment-related morbidity												
0	-	-	-	-	-	-	-	-	-	-	-	-
Treatment-related mortality												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life: 1 year post-treatment												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Low number of events. 2 Most patients entered in the trial (53%) embargoed for administrative reasons in one of the participating institutions.

Cost-effectiveness evidence (see also Appendix E) (2014)

Background and aims

The role of low dose rate (LDR) or high dose rate (HDR) brachytherapy in locally advanced or high risk disease is unclear. Recently published randomised trials have established that, in patients with locally advanced prostate cancer, external beam radiotherapy (EBRT) in combination with hormone therapy is now standard treatment. However, it has been postulated that a combination of brachytherapy (either LDR or HDR) and EBRT may be more effective.

Aims

This economic evaluation aimed to assess the cost-effectiveness of LDR or HDR brachytherapy in combination with external beam radiotherapy. The analysis considered the perspective of the National Health Service (NHS).

Methods

Economic evidence review

A systematic literature review did not identify any existing evidence that sufficiently addressed the current decision problem. However, a currently unpublished report (Lord *et al* [under review]) on the use of full pathway models in guideline development included an analysis that does address the decision problem. This analysis was conducted by the London School of Hygiene and Tropical Medicine (LSHTM) and is based on the same model that was adapted to investigate the use of MRI before initial biopsy (see Appendix B).

The results of the analysis suggested that brachytherapy monotherapy was more cost-effective than HDR brachytherapy plus EBRT, LDR brachytherapy plus EBRT and radiotherapy plus hormone therapy. Indeed, brachytherapy monotherapy was found to be the dominant strategy providing the highest expected QALY gain and the lowest cost.

However, this modelling exercise was primarily intended to be an illustration of how full pathway models might be applied in guideline development. As such, there are limitations with the analysis. Most notably, the clinical data used to inform the effectiveness of the interventions were drawn from disparate sources and were sometimes at odds with the directly comparable data available.

De novo economic model

Since the economic analysis in its original form did not adequately address the decision problem, the model was adapted and an updated analysis was performed. The primary changes were made to the clinical evidence used to inform the effectiveness of the interventions and to the costs used in the analysis, which were updated to reflect a more recent price year (2011/12).

The results of the clinical evidence review were used to inform the efficacy of the interventions in the model. Since no high quality evidence was identified on the use of LDR brachytherapy in combination with EBRT, this intervention was not modelled. Instead, the analysis was focused on the areas where RCT evidence was available. Thus, only a comparison of HDR brachytherapy in combination with EBRT versus EBRT alone was modelled using the results of two RCTs (Sathya *et al*. 2005 and Hoskin *et al* 2012). However, it should be noted that, although these RCTs provide the best evidence currently available, they do lack some applicability to current practice. Both studies used lower doses in their

Update 2014

EBRT-only arms (66 Gy and 50 Gy respectively) (Sathya *et al*. 2005; Hoskin *et al*. 2012) than the minimum of 74 Gy recommended in the 2008 NICE prostate cancer guideline.

Both RCTs suggested that biochemical failure free survival was improved when men were treated with EBRT in combination with HDR brachytherapy compared to EBRT alone, while there was no clear difference observed in overall survival. The effectiveness data (biochemical free survival) from these studies were modelled individually as two separate scenarios using pre-loaded effectiveness data in the LSHTM model (Scenario 1: Sathya *et al*. 20052 and Scenario 2: Hoskin *et al*. 2007).

In terms of treatment related morbidity, the RCTs showed that gastrointestinal complications occurred in 6% and 4% of men treated with EBRT in combination with HDR brachytherapy and EBRT alone, respectively (Sathya *et al*. 2005; Hoskin *et al*. 2012). Genitourinary complications were found to occur in 22% and 19% of men treated with EBRT in combination with HDR brachytherapy and EBRT alone, respectively (Sathya *et al*. 2005; Hoskin *et al*. 2012). The proportion of patients suffering with sexual dysfunction was estimated using data from Sathya *et al*. 2005, which suggested that sexual dysfunction occurred in 69% and 68% of men treated with EBRT in combination with HDR brachytherapy and EBRT alone, respectively (Sathya *et al*. 2005).

Costs and benefits in the model are calculated as the model progresses. The costs reflect the monitoring, management or treatment strategies that the patient is currently receiving, including drug costs, treatment costs or any other resource use that may be required (e.g. GP visit). The majority of costs were sourced from NHS reference costs 2011/12 (NHS reference costs 2011-2012) by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dose and unit cost information from the British National Formulary (BNF) (Joint Formulary Committee), resource use and cost information from the Personal Social Services Research Unit (PSSRU) (Curtis 2012) and the advice of the GDG. The costs associated with radiotherapy treatment strategies were estimated using the doses reported in the RCTs (Sathya *et al*. 2005 and Hoskin *et al*. 2007/12) and unit costs from NHS reference costs 2011/12 (NHS reference costs 2011-2012).

Update 2014

In terms of benefits, each health stage of disease has an associated quality of life (QoL) value. This reflects the model's measurement of benefits in terms of QALYs, whereby the quantity and quality of life can be expressed simultaneously. All utility estimates were sourced from published studies, with an effort made to best reflect the appropriate patient population (Korfage *et al*. 2005; Volk *et al*. 2004).

The overall costs and benefits for each treatment are then estimated based on the total length of time individuals spend in each health state over the modelled time horizon. Costs and benefits were discounted at 3.5% per year as recommended by NICE.

Results

The results of the model when running scenarios 1 and 2 are shown in Tables 32 and 33, respectively. It should be noted that as the results represent the full prostate cancer treatment pathway, the absolute values presented should be interpreted with caution. However, importantly, the incremental results can be interpreted in the usual way. Furthermore, note that one-way sensitivity analysis and probabilistic sensitivity analysis has not been conducted for this analysis. This is because the topic was not originally intended to be modelled and as such modelling priorities lie elsewhere. Furthermore, the GDG felt that there were significant limitations with the evidence base in this area and that running further analyses with this data would be of limited use in the decision making process.

The ICER results for scenario 1 and scenario 2 show that EBRT in combination with HDR brachytherapy is more effective and more expensive than EBRT alone. Furthermore, the tables show that one additional QALY is provided at a cost of £2,804 and £3,931 in scenario 1 and 2, respectively. Thus, as these figures are below a commonly accepted willingness to

pay (WTP) threshold of £20,000 per QALY, EBRT in combination with HDR brachytherapy would be considered cost-effective in both scenarios.

Table 32: Total expected costs, QALYs and ICER per individual patient in scenario 1

Outcome	EBRT+HDR brachytherapy	EBRT only	Incremental
Total costs	£8,572	£8,250	£322
Total LYs	10.06	9.99	0.07
Total QALys	8.82	8.70	0.11
ICER (cost per QALY)			**£2,804**

Table 33: Total expected costs, QALYs and ICER per individual patient in scenario 2

Outcome	EBRT+HDR brachytherapy	EBRT only	Incremental
Total costs	£8,305	£8,128	£177
Total LYs	10.07	10.04	0.03
Total QALys	8.82	8.78	0.04
ICER (cost per QALY)			£3,931

Conclusion

In conclusion, the economic analysis suggests that HDR brachytherapy in combination with EBRT is a cost-effective use of resources. However, there are concerns about the applicability of the evidence upon which this conclusion is based because of doses used in the RCTs. Further research is required that investigates the cost-effectiveness of the strategies when using doses that would be typical of clinical practice and considers equivalent overall doses in both arms.

Update 2014

Recommendations	**Consider high-dose rate brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer. [new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of overall survival, disease-free survival, biochemical disease-free survival, treatment-related morbidity, treatment-related mortality and health-related quality of life to be the most important in determining if the combination of high- or low-dose rate brachytherapy with external beam radiotherapy was more effective than either intervention alone for men with localised or locally advanced non-metastatic prostate cancer. The outcomes of disease-free survival and treatment-related mortality were not reported for any of the comparisons of interest. Of the other outcomes, only biochemical disease-free survival and treatment-related morbidity were consistently reported across all comparisons of interest. None of the evidence reported outcomes according to different risk groups. No evidence was found comparing high-dose rate brachytherapy plus external beam radiotherapy with high-dose rate brachytherapy alone.
Quality of the evidence	For the comparison of high-dose rate brachytherapy plus external beam radiotherapy with external beam radiotherapy alone, the RCT evidence was assessed by GRADE as low quality for the outcome of treatment-related morbidity and moderate quality for the outcomes of biochemical disease-free survival, overall survival and health-related quality of life. A

	meta-analysis of non-randomised studies was assessed as very low quality for the outcomes of overall survival and biochemical disease-free survival. For low-dose rate brachytherapy plus external beam radiotherapy compared to both external beam radiotherapy alone and low-dose rate brachytherapy alone, the evidence was assessed by GRADE as very low quality for the outcomes of biochemical disease-free survival and treatment related morbidity. The GDG noted that the control arms in the trials included in the evidence base, used a lower dose of radiotherapy, which had been previously shown to be inferior to that used in current clinical practice. The GDG were therefore aware that there was some uncertainty over the effectiveness of external beam radiotherapy alone compared to the combined treatment, because the trials had used a lower dose of radiotherapy
Trade-off between clinical benefits and harms	The GDG noted that the evidence comparing high-dose rate brachytherapy plus external beam radiotherapy with external beam radiotherapy alone had shown improved biochemical disease-free survival without an increase in adverse events for the combined treatment. Taking into consideration the uncertainty over the effectiveness of external beam radiotherapy alone (compared to combined treatment), the GDG decided to recommend that high-dose rate brachytherapy plus external beam radiotherapy be considered as a treatment option. The GDG agreed that it was not possible to make recommendations on any other treatment combinations due to the low quality and limited data available.
Trade-off between net health benefits and resource use	The GDG noted that both the base case for the health economic analysis and the sensitivity analysis had shown that combined high-dose rate brachytherapy plus external beam radiotherapy was cost-effective at a willingness to pay threshold of £20,000/QALY.

Update 2014

Research recommendation	**What is the effectiveness of androgen deprivation therapy or brachytherapy, in combination with radiotherapy, for men with intermediate- and high-risk localised non-metastatic prostate cancer? [2014]**
Why is this important	There is insufficient evidence comparing brachytherapy or adjuvant androgen deprivation therapy in combination with external beam radiotherapy, with the current optimal techniques using external beam radiotherapy alone for men with intermediate and high risk localised non-metastatic prostate cancer.

4.4.7 HIFU and cryotherapy

HIFU and cryotherapy have recently become options requiring evaluation.

HIFU and cryotherapy aim respectively to eradicate prostate cancer by heating the gland using ultrasound or by freezing it. Both technologies have been the subject of NICE Interventional Procedure Guidance on their use as primary therapy and for men with recurrent disease (NICE 2005a, 2005b, 2005c). Although they have been assessed for use on the basis of safety and efficacy, the guidance documents drew attention to the lack of evidence on quality of life and long term survival.

Recommendation	**Do not offer high-intensity focused ultrasound and cryotherapy to men with localised prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions.[k] [2008]**
Qualifying statement	There is insufficient evidence of the clinical and cost effectiveness of cryotherapy and HIFU in comparison to established interventions to recommend their routine use.

Clinical evidence (2008)

Cryotherapy

Evidence comes from three systematic reviews of case series (Hummel *et al*. 2003; National Institute for Health and Clinical Excellence 2005; Shelley *et al*. 2007) and two Canadian randomised trials (Donnelly *et al*. 2007; Chin *et al*. 2007) comparing cryotherapy to external beam radiotherapy. The reviews concluded that evidence was of poor quality: the length of follow-up was very limited so there was no good evidence about disease specific or overall survival. The intermediate end-points of biochemical recurrence and prostate biopsy, however, show that cryotherapy ablates prostate tissue. Treatment toxicity was also reported: most commonly sexual dysfunction and stress incontinence.

Both the randomised trials failed to enrol the planned number of patients, and their results should be viewed with caution. The results of one trial (Chin *et al*. 2007) suggested a greater risk of biochemical failure with cryotherapy than with external beam radiotherapy. The other trial (Donnelly *et al*. 2007), published as an abstract only, did not find a statistically significant difference in the rate of treatment failure in the first three years after treatment. Neither trial reported a difference in the overall survival of the cryotherapy and radiotherapy groups.

HIFU

All the included studies were case series (Chaussy & Thuroff 2003; Beerlage *et al*. 1999; Ficarra *et al*. 2006; Ganzer *et al*. 2007; Gelet *et al*. 1999; Gelet *et al*. 2000; Lee *et al*. 2006; Poissonnier *et al*. 2003; Poissonnier *et al*. 2007; Thuroff *et al*. 2003; Uchida *et al*. 2002; Uchida *et al*. 2005; Uchida *et al*. 2006). Follow-up in these series was short, most had a median follow-up of less than two years. This means that disease specific or overall survival data are lacking for HIFU. The intermediate outcomes of biochemical recurrence and prostate biopsy suggest that HIFU ablates prostate tissue. Treatment toxicities associated with HIFU included sexual dysfunction, stress incontinence, urethral strictures and urinary tract infection.

Technical developments in both cryotherapy and HIFU procedures, mean that results from the earlier series may not be applicable to current practice.

k NICE interventional procedures guidance 118, 119 and 145 evaluated the safety and efficacy of cryotherapy and high intensity focused ultrasound for the treatment of prostate cancer. NICE clinical guidelines provide guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS. As there was a lack of evidence on quality of life benefits and long-term survival. these interventions are not recommended in this guideline.

Research recommendation	**Research is required into the effectiveness and cost-effectiveness of treatments aimed at the elimination of disease in men with localised prostate cancer, with locally advanced disease and with locally recurrent disease. This research should include a rigorous examination of the value of procedures such as brachytherapy (localised disease only), cryosurgery and high intensity focused ultrasound, as well as combinations of surgery and radiotherapy with hormonal therapy and chemotherapy. The end points should include survival, local recurrence, toxicity and quality of life outcomes. [2008]**
Why is this important	A wide and growing range of radical therapies aimed at the eradication of disease are available. Although long-term follow-up data are available for some of these in the localised disease setting, there have been no randomised trials comparing these treatments and there is little evidence to support their use in locally advanced recurrent disease.

4.5 Managing adverse effects of treatment

Treatment of men with localised prostate cancer may be associated with a wide range of significant adverse effects. Adverse effects are commonly classified according to their timing. Acute effects are those which typically occur within days or weeks of treatment. Late effects occur months or even years after treatment. It is not possible to provide comprehensive guidance on the management of all possible complications of treatment. Instead, this guideline focuses on those adverse effects which are important because they are common, long-lasting and may seriously affect quality of life: rectal problems after radiotherapy, sexual dysfunction and urinary incontinence.

Recommendation	**Given the range of treatment modalities and their serious side effects, men with prostate cancer who are candidates for radical treatment should have the opportunity to discuss their treatment options with a specialist surgical oncologist and a specialist clinical oncologist. [2008]**
Qualifying statement	In the absence of any evidence there was GDG consensus that men's decisions should be informed by site specialist clinicians.

4.5.1 Rectal problems after radiotherapy

4.5.1.1 Radiation induced enteropathy

Radiotherapy for prostate cancer may lead to a range of adverse effects on the bowel. Men receiving radiotherapy to pelvic lymph nodes may experience problems from irradiation of the small bowel. More commonly, radiotherapy is targeted at the prostate alone (and not the lymph nodes) and it is the rectum that is at risk of radiation effects.

Acute and late toxicity in the rectum and bowel is a significant complication of radiotherapy for prostate cancer. Many men develop acute rectal symptoms during and shortly after radiotherapy. These are usually self-limiting but very occasionally can be severe and prolonged. A small proportion of men may have radiation-induced injury, with or without anatomical disturbance, which may lead to significant long term symptoms.

Many interventions have been tried to prevent or treat bowel complications of radiotherapy- for acute side-effects, changes in diet, anti-diarrhoeal agents (loperamide, lomotil) and rectal steroids are commonly used, and have the advantages of being relatively cheap and readily available, but interventions such as aminosalicylates (sulphasalazine), sucralfate and somatisation analogues (octreotide) have also been investigated. For late effects, rectal

Update 2014

sucralfate, rectal steroids, dietary changes and interventions such as thermal coagulation have been examined.

Clinical question: What is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all outcomes is summarised in Tables 34 – 45.

Bowel toxicity: prophylactic

Seven low quality studies were indentified which assessed a variety of diets for bowel toxicity compared to a control group. In one study significantly fewer patients reported diarrhoea in the diet group (23% versus 48%; p<0.01) and took less anti-diarrhoeal medication (mean 0.6 tablets per day versus 1.1, p<0.01). However, at 12 months there were no differences between groups (Bye *et al*. 1992). Another study reported lower rates of grades 1 and 2 diarrhoea in the diet group (16.5% versus 25.1% and 11.9% versus 27.2% respectively) (Capirci *et al*. 2000). One study also provided evidence of a significantly lower risk of, and increase in grade of, acute diarrhoea at the end of treatment (p=0.04) (Arregui Lopez *et al*. 2012). None of the other studies reported a beneficial effect of dietary interventions on gastrointestinal symptoms following pelvic radiotherapy. These studies had relatively small sample sizes and patients were non-blinded to their treatment allocation.

Four studies of very low quality compared probiotic supplements with a placebo control in the prevention of radiation-induced diarrhoea. The pooled analysis yielded an RR of 0.73 (95% CI 0.35-1.53) for any grade of diarrhoea during radiotherapy. As reported in the meta-analysis by Fuccio *et al*. (2009) for diarrhoea of Grade 3 or above, three of these studies do not provide definitive conclusions that probiotic supplementation may be effective for the prevention of radiation-induced diarrhoea (RR 0.37; 95% CI 0.04-3.27). Two studies reported 25% versus 30.6% patients required anti-diarrhoeal medication in the probiotic and control groups respectively (RR 0.66; 95% CI 0.16-2.77). One study reported that survival at 60 days without grade > 2 diarrhoea was 35% versus 27% for the standard dose and high dose probiotic groups compared to 17% for the placebo group (HR 0.69; p=0.04 for standard dose versus placebo) (Germain *et al*. 2011). No significant difference was found between standard dose and placebo for the incidence of grade > 3 diarrhoea.

One very low quality study reported that patients receiving the probiotic '5' strain dophilus were more likely to have ≥ 4 daily bowel movements but were less likely to need anti-diarrhoeal medication than patients taking the probiotic Hylak Tropfen (Timko *et al*. 2010).

One study of moderate quality evaluated the rectal toxicity data of men being treated for localised prostate cancer who took part in a trial of aerobic exercise (Kapur *et al*. 2010). There were no differences in mean rectal toxicity scores at the 4-week post-treatment review (MD 0.19 lower (0.57 lower to 0.19 higher).

One moderate quality study compared a glucocorticosteroid beclomethasone dipropionate (BDP) enema with a placebo (Fuccio *et al*. 2011). There was no significantly beneficial effect of BDP on bowel toxicity based on the RTOG/EORTC toxicity scales, or for the bowel frequency and urgency of defecation items of the SCCAI. Blood in the stool was present at least once per week in 22% versus 42% of BDP and placebo groups respectively (RR 0.51; 95% CI 0.29-0.92). Placebo patients were more likely than intervention patients to develop grade 2 or higher toxicity as assessed by endoscopy and the Vienna Rectoscopy Score (VRS) (RR 0.59; 95% CI 0.41-0.85).

Update 2014

One meta-analysis of six RCTs did not show a benefit of sucralfate for the prevention of acute diarrhoea after pelvic EBRT (RR 0.96; 95% CI 0.81-1.14) (Hovdenak *et al*. 2005). However, some of the trials noted increased bowel toxicity in the patients treated with sucralfate.

Bowel toxicity: treatment

One RCT found patients receiving 1 week of probiotic supplementation needed anti-diarrhoeal medication less frequently than the placebo group, but the difference was not significant (Urbancsek *et al*. 2001). There were also no significant differences in number of bowel movements and rating of diarrhoea between the two groups at follow-up.

Two studies of low and very low quality reported the use of hyperbaric oxygen therapy (HBOT) for the treatment of radiation-induced toxicity, similar scores were found between groups using LENT-SOMA scoring system. Another study found 45% versus 27% of the HBOT and control groups achieved complete resolution or significant improvement of proctitis (RR 1.69; 95% CI 1.02-1.82) (Clarke *et al*. 2008).

One study of moderate quality compared Pentosanpolysulfate (PPS – a substance similar to sulfracate) to a placebo for the treatment of radiation-induced toxicity and found no beneficial effect (Pilepich *et al*. 2006). Another study, reported in a systematic review, found sulfracate showed greater improvement compared to anti-inflammatories for clinical features (RR 1.76 95% CI 1.08-2.87) (Kochhar *et al*. 1991). For endoscopic features no discernable difference was detected between groups. While Chruscielewska-Kiliszek *et al*. (2012) found low quality evidence that the improvement in chronic radiation proctitis or endoscopy scores (overall severity, diarrhea, bleeding, or tenesmus) at 8, 16 and 52 weeks did not significantly differ between patients receiving sucralfate or placebo after APC.

Update 2014

One unpublished study provided low quality evidence of the effects of Argon Plasma Coagulation (APC) versus topical formalin for treating rectal bleeding after radiation therapy for carcinoma of the bladder (Botten *et al*. 2011). Rectal bleeding was improved in all 29 patients after a median of 2 (range 1-4) sessions of Formalin, or 1.5 (range 1-4) sessions of APC treatment. No differences in the efficacy of the two treatments were observed. A second low quality study found a significant improvement in rectal bleeding and bowel frequency at 8 weeks following formalin application (Sahakitrungruang *et al*. 2012). However, there was also significant improvement in rectal bleeding, bowel frequency, urgency, diarrhea, and tenesmus in the comparator group at 8 weeks following colonic irrigation and antibiotics. This resulted in a significantly greater improvement in rectal bleeding, urgency, and diarrhoea in the colonic irrigation group.

One study provided low quality evidence of the effectiveness of a sucralfate-steroid enema versus topical formalin in the treatment of radiotherapy induced bowel toxicity (Nelamangala *et al*. 2012). Patients experiencing rectal bleeding in both groups experienced a significant decrease in symptom (measured using the Radiation Proctopathy System Assessment Scale (RPSAS)) and sigmoidoscopic scores at 4 weeks ($p<0.001$). There was no significant difference between the groups in the number of patients reaching and maintaining an improvement in symptom score and sigmoidoscopy grade.

Treatment-related morbidity

One study reported ear pain and discomfort in 15.8% of patients following HBOT (Clarke *et al*. 2008). Of these, 7 had tympanic membrane changes consistent with barotraumas, and 1 had both tympanic membrane injury and middle ear effusion. 7 underwent ventilation tube replacement. Two patients (1.7%) complained of confinement anxiety.

Chruscielewska-Kiliszek *et al*. (2012) found low quality evidence of severe constipation (7%) and urticaria (2%) in patients receiving sucralfate following APC compared to no complications in the placebo group.

One low quality study comparing formalin application to colonic irrigation and antibiotics reported that 20 (80%) patients in the formalin group experienced anorectal discomfort during application and six (24%) patients in the colonic irrigation group experienced nausea due to antibiotic use (Sahakitrungruang *et al*. 2012).

One study providing low quality evidence of the effectiveness of a sucralfate-steroid enema versus topical formalin also reported mild pain in 33.3% of patients during formalin application and no complications following the sucralfate-steroid enema (Nelamangala *et al*. 2012).

Colostomy rate

This outcome was not reported by any of the included studies.

Health-related quality of life: prophylactic

Two studies reported the effects of dietary interventions on quality of life with no significant differences between intervention and control groups. One study found there was less decrease in the quality of life of patients (measured using the FACIT-D) in the diet group compared to the control at 3 weeks, but not after completion of the radiotherapy (Arregui Lopez *et al*. 2012).

One study showed a similar improvement in mean quality of life scores between those receiving probiotic supplements and control group patients (MD 3.70 higher (1.21 lower to 8.61 higher)) (Giralt *et al*. 2008).

Mean quality of life scores were found to be higher at 12 month follow-up for patients receiving BDP than patients in the placebo group (Fuccio *et al*. 2011). In both groups IBDQ scores decreased over time although the reduction was more pronounced in the placebo group (p=0.034). This difference may have been due to the higher rates of rectal bleeding in the placebo group.

Health-related quality of life: treatment

Two studies reported an improvement of health related quality of life in both HBOT and control groups, with a greater improvement in the former. In Clarke *et al*. (2008) the mean Bowel Bother and Bowel Function scores after treatment were 59.96 versus 59.74 and 69.82 versus 68.30 for the HBOT and control groups respectively. In Sidik *et al*. (2007) the percentage mean difference in quality of life scores before and after the intervention was 19.67 versus 4.53 respectively (p<0.001).

One moderate quality study found no beneficial effect of PPS compared to placebo on quality of life (RR 0.80 95% CI 0.46 to 1.39).

Update 2014

Table 34: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: dietary intervention versus control

Quality assessment							Number of patients		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dietary intervention	Control	Relative	95% CI	Absolute	
Bowel toxicity (measured using IBDQ-B, QLQ-C30, RTOG and VIS)												
7	RCTs	Serious[1]	None	Serious[2]	None	None	613*	589*	-	-	Not pooled	LOW ☐☐☐☐
Treatment-related morbidity												
0	-	-	-	-	-	-	-	-	-	-	-	-
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life (measured using IBDQ and QLQ-C30)												
4	RCTs	Serious[1]	None	Serious[3]	None	None	182*	143*	-	-	Not pooled	LOW ☐☐☐☐

**Better results indicated by lower values. 1 Patients and investigators were non-blinded to group allocation. Patient reported own symptoms which increases bias. 2 Five studies included patients with cancers other than prostate cancer. 3 Studies included patients with cancer other than prostate cancer.*

Table 35: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: probiotics versus control

Quality assessment							Number of patients		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics	Control	Relative	95% CI	Absolute	
Bowel toxicity: radiation-induced diarrhoea (any grade) (assessed using NCI-CTC/WHO grading)												
4	RCTs	Serious[1]	None	Serious[2]	Serious[3]	None	142 / 330 (43.0%)	188 / 321 (58.6%)	RR 0.73	(0.35 – 1.53)	158 fewer per 1,000 (from 381 fewer to 310 more)	VERY LOW
Bowel toxicity: radiation-induced diarrhoea (grade 3 or higher) (assessed using NCI-CTC/WHO grading)												
3	RCTs[4]	Serious[1]	None	Serious[2]	Serious[3]	None	28 / 319 (8.8%)	85 / 311 (27.3%)	RR 0.37	(0.04 – 3.27)	172 fewer per 1,000 (from 262 fewer to 620 more)	VERY LOW
Bowel toxicity: anti-diarrhoeal drug used												
2	RCTs	Serious[5]	None	Serious[6]	Serious[7]	None	19 / 76 (25.0%)	22 / 72 (30.6%)	RR 0.66	(0.16 – 2.77)	104 fewer per 1,000 (from 257 fewer to 541 more)	VERY LOW
Treatment-related morbidity												
0	-	-	-	-	-	-	-	-	-	-	-	-
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life (measured using EORTC QLQ mean change in score (range 0-100))												
1	RCT	Serious[8]	None	Serious[9]	Serious[10]	None	39*	33*	Not reported	Not reported	MD 3.70 higher (from 1.21 lower to 8.61 higher)	VERY LOW

**Better results indicated by lower values. 1 The generation of allocation sequence and concealment of treatment allocation were not reported in any of the studies. None of the studies employed an intent-to-treat analysis or reported being sufficiently powered. 2 None of the studies included prostate cancer patients only. Other tumour sites include the rectum and cervix. The four studies assessed the prophylactic use of probiotics for the prevention of acute radiation-induced diarrhoea, rather than treatment of radiation-induced bowel toxicity. 3 Total number of events in less than 300. The confidence interval suggests there could be little difference between probiotics and control. 4 Giralt et al. 2008, Delia et al. 2007 and Salminen et al. 1998 reported in meta-analysis by Fuccio et al. 2009. 5 Studies do not report method of blinding or allocation concealment. Lack of power calculations and intent-to-treat analysis. 6 Both studies included female participants with gynaecological cancers. 7 Few events, small sample*

size and wide confidence intervals suggest imprecise data. 8 Method of allocation concealment and blinding not stated. Study was prematurely terminated and did not reach calculated sample size to acheive 80% power. 9I ncluded female participants with cervical or endometrial cancer only. Explored the use of probiotics in preventing radiation-induced diarrhoea. 10 Very wide confidence intervals suggests imprecise data.

Table 36: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: '5' strain dophilus versus hylak tropfen forte

Quality assessment							Number of patients		Effect			Quality
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**'5' strain dophilus**	**Hylak tropfen forte**	**Relative**	**95% CI**	**Absolute**	
Bowel toxicity: ≥ 4 mean bowel movements per day (follow-up 5 weeks) (patient reported)												
1	RCT	Serious[1]	None	Serious[2]	Serious[3]	None	9 / 22 (40.9%)	4 / 20 (20.0%)	RR 2.05	(0.74 – 5.62)	210 more per 1,000 (from 52 fewer to 924 more)	VERY LOW
Bowel toxicity: anti-diarrhoeal medication (follow-up 5 weeks) (patient reported)												
1	RCT	Serious[1]	None	Serious[2]	Serious[3]	None	6 / 22 (27.3%)	11 / 20 (55.0%)	RR 0.50	(0.23 – 1.09)	275 fewer per 1,000 (from 424 fewer to 50 more)	VERY LOW
Treatment-related morbidity												
0	-	-	-	-	-	-	-	-	-	-	-	-
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Unclear whether patients or investigators were blind to treatment allocation. Authors state that groups were not balanced with regards to gender and primary tumour site. Method of allocation concealment not stated.
2 Patients included those with cancers other than prostate cancer. No control group.
3 Small sample size and number of events reduces confidence in precision of results.

Table 37: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: exercise versus control

Quality assessment							Number of patients		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	Control	Relative	95% CI	Absolute	
Bowel toxicity: (follow-up 4 weeks) (measured using RTOG/EORTC scales (range 0-3))												
1	RCT	None	Serious[1]	None	None	None	32*	33*	-	-	MD 0.19 lower (from 0.57 lower to 0.19 higher)	MODERATE
Treatment-related morbidity												
0	-	-	-	-	-	-	-	-	-	-	-	-
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

**Better results indicated by lower values. 1 Due to the lack of studies and small sample size it is not possible to be confident in the degree of consistency for this outcome.*

Table 38: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: beclomethasone diproprionate (BDP) versus control

Quality assessment							Number of patients		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BDP	Control	Relative	95% CI	Absolute	
Bowel toxicity (any grade) (follow-up 12 months) (measured using RTOG/EORTC scales)												
1	RCT	None	None	None	Serious[1]	None	24 / 55 (43.6%)	28 / 59 (47.5%)	RR 0.92	(0.61 – 1.38)	38 fewer per 1,000 (from 185 fewer to 180 more)	MODERATE
Bowel toxicity (grade 2 or above) (follow-up 12 months) (measured using Endoscopy VRS)												
1	RCT	None	None	None	Serious[1]	None	22 / 55 (40.0%)	40 / 59 (67.8%)	RR 0.59	(0.41 – 0.85)	278 fewer per 1,000 (from 102 fewer to 400 fewer)	MODERATE
Bowel toxicity: > 3 mean bowel movements per day (follow-up 12 months) (measured using SCCAI)												
1	RCT	None	None	None	Serious[1]	None	4 / 55 (7.3%)	4 / 59 (6.8%)	RR 1.07	(0.28 – 4.08)	5 more per 1,000 (from 49 fewer to 209 more)	MODERATE
Bowel toxicity: urgency of defecation (follow-up 12 months) (measured using SCCAI)												
1	RCT	None	None	None	Serious[1]	None	11 / 55 (20.0%)	13 / 59 (22.0%)	RR 0.91	(0.44 – 1.85)	20 fewer per 1,000 (from 123 fewer to 187 more)	MODERATE
Bowel toxicity: blood in stool (follow-up 12 months) (measured using SCCAI)												
1	RCT	None	None	None	Serious[1]	None	12 / 55 (21.8%)	25 / 59 (42.4%)	RR 0.51	(0.29 – 0.92)	208 fewer per 1,000 (from 34 fewer to 301 fewer)	MODERATE
Treatment-related morbidity												
0	-	-	-	-	-	-	-	-	-	-	-	-
Colostomy rate												

Quality assessment							Number of patients		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BDP	Control	Relative	95% CI	Absolute	
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life (follow-up 12 months) (measured using IBDQ change score)												
1	RCT	None	None	None	None	None	55*	59*	-	-	Not pooled	HIGH

1 **Better results indicated by lower values. 1 Wide confidence intervals and low event rate suggest imprecision.*

Table 39: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: sucralfate versus control

Quality assessment							Number of patients		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sucralfate	Control	Relative	95% CI	Absolute	
Bowel toxicity: grade 2-3 diarrhoea												
8	RCTs	None[1]	None[2]	Serious[3]	None	None	146 / 345 (42.3%)	157 / 358 (43.9%)	RR 0.96	(0.81 – 1.14)[4]	18 fewer per 1,000 (from 83 fewer to 61 more)	LOW
Bowel toxicity: change in chronic radiation proctitis score												
1	RCT	None	None	Serious[5]	Serious[6]	None	-	-	-	-	-	LOW
Treatment-related morbidity												
0	-	-	-	-	-	-	-	-	-	-	-	-
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Eight trials as reported in meta-analysis by Hovnedak et al. 2005. Trials were double-blind. No information about allocation concealment.
2 Large differences in the effects between studies. Three trials suggest benefit and three trials suggest harm.
3 Three trials include patients with cancers other than prostate cancer, including gynaecological cancers.
4 The data from 6 trials were pooled. Two trials reported data that were unsuitable for meta-analysis. Placebo patients required more anti-diarrhoea medication.
5 Not limited to patients with prostate carcinoma.
6 Only 122 patients included in the study.

Table 40: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: probiotics versus placebo

Quality assessment							Number of patients		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics	Placebo	Relative	95% CI	Absolute	
Bowel toxicity: anti-diarrhoeal medication												
1	RCT	None	None	Serious[1]	Serious[2]	None	36 / 102 (35.3%)	49 / 103 (47.6%)	RR 0.74	(0.53 – 1.03)	124 fewer per 1,000 (from 224 fewer to 14 more)	LOW
Bowel toxicity: average number of bowel movements												
1	RCT	None	None	Serious[1]	Serious[2]	None	-	-	-3	-	-	LOW
Bowel toxicity: diarrhoea (assessed using Investigator ratings scale (range 0-3))												
1	RCT	None	None	Serious[1]	Serious[2]	None	-	-	-4	-	-	LOW
Treatment-related morbidity												
0	-	-	-	-	-	-	-	-	-	-	-	-
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Around 75% of participants were female patients with gynaecological cancers. 2 Few events and small sample size. No power calculations. 3 Probiotics=2.4, Placebo=3.2 (non-significant difference). 4 Probiotics=0.7, Placebo=1.0 (non-significant difference).

Table 41: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: hyperbaric oxygen therapy (HBOT) versus control

Quality assessment							Number of patients		Effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBOT	Control	Relative	95% CI	Absolute	Quality
Bowel toxicity (assessed using SOMA-LENT)												
2	RCTs	Serious[1]	None	Serious[2]	None	None	110*	115*	Not reported	Not reported	Not pooled	LOW
Bowel toxicity: complete or significant improvement (assessed using clinical evaluation)												
1	RCT	Serious[3]	None	Serious[4]	Serious[5]	None	29 / 64 (45.3%)	15 / 56 (26.8%)	RR 1.69	(1.02 – 1.82)	185 more per 1,000 (from 5 more to 220 more)	VERY LOW
Treatment-related morbidity: patient reported ear pain												
1	RCT	Serious[3]	None	Serious[4]	None	None	19 / 64 (29.7%)	0 / 56 (0.0%)	Not reported	Not reported	Not pooled	LOW
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life (assessed using Bowel Bother subscale)												
1	RCT	Serious[3]	None	Serious[4]	Serious[6]	None	64*	56*	Not reported	Not reported	Not pooled	VERY LOW
Health-related quality of life (assessed using Karnofsky scale)												
1	RCT	Serious[3]	None	Serious[7]	Serious[6]	None	0*	-	Not reported	Not reported	Not pooled	VERY LOW

**Better results indicated by lower values. 1 Blinding procedure and allocation concealment not specified in Sidik et al. 2007. No details of intervention procedure and poorly reported results. 2Both studies included female participants with gynaecological cancers. 3 No intent-to-treat analysis. Results highly sensitive to allocation of dropouts. 4 Patients include women with gynaecological cancers. 5 Low event rate. 6 Wide confidence intervals/standard deviations. 7 All participants are cervical cancer patients*

Table 42: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: pentosanpolysulfate (PPS) versus control

Quality assessment							Number of patients		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PPS	Control	Relative	95% CI	Absolute	
Bowel toxicity: improvement (follow-up 3 months) (assessed using NCI CTC)												
1	RCT	None	None	Serious[1]	None	None	40 / 98 (40.8%)	24 / 53 (45.3%)	RR 0.90	(0.62 – 1.32)	45 fewer per 1,000 (from 172 fewer to 145 more)	MODERATE □□□□
Treatment-related morbidity												
0	-	-	-	-	-	-	-	-	-	-	-	-
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life: improvement (follow-up 3 months) (assessed using SQLI)												
1	RCT	None	None	Serious[1]	None	None	23 / 86 (26.7%)	14 / 42 (33.3%)	RR 0.80	(0.46 – 1.39)	67 fewer per 1,000 (from 180 fewer to 130 more)	MODERATE □□□□

1Study included patients with cancers other than prostate cancer. Pentosanpolysulfate is a substance similar to Sucralfate.

Table 43: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: sucralfate versus anti-inflammatory

Quality assessment							Number of patients		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sucralfate	Anti-inflammatory	Relative	95% CI	Absolute	
Bowel toxicity (assessed using clinical features)												
1	RCT[1]	Serious[2]	None	Serious[3]	Serious[4]	None	16 / 17 (94.1%)	8 / 15 (53.3%)	RR 1.76	(1.08 – 2.87)	405 more per 1,000 (from 43 more to 997 more)	VERY LOW
Bowel toxicity (assessed using endoscopic features)												
1	RCT[1]	Serious[2]	None	Serious[3]	Serious[4]	None	12 / 17 (70.6%)	7 / 15 (46.7%)	RR 1.51	(0.81 – 2.82)	238 more per 1,000 (from 89 fewer to 849 more)	VERY LOW
Treatment-related morbidity												
0	-	-	-	-	-	-	-	-	-	-	-	-
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Kochhar et al. 1991 as presented in the systematic review by Denton et al (2009). 2 Method of randomisation is not stated nor whether the assessors were blinded. 3 35/36 patients were females treated for cervical cancer. 4 Small sample size and few events.

Table 44: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: formalin versus comparator

Quality assessment							Number of patients		Effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Formalin	Comparator	Relative	95% CI	Absolute	Quality
Bowel toxicity: rectal bleeding – comparator colonic irrigation + anti-biotics												
1	RCT	None	None	Serious[1]	Serious[2]	None	4 / 25 (16.0%)	1 / 25 (4.0%)	RR 4.0	(0.5 – 33.3)	120 more per 1,000 (from 20 fewer to 1,292 more)	LOW
Bowel toxicity: rectal bleeding – comparator APC												
1	RCT	Serious[3]	None	None	Serious[4]	None	Not reported	Not reported	Not reported	Not reported	Not pooled	LOW
Treatment-related morbidity												
1	RCT	None	None	Serious[1]	Serious[2]	None	Not reported	Not reported	Not reported	Not reported	Not pooled	LOW
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Not limited to patients who have undergone radiotherapy for prostate cancer. 2 Less than 100 patients in study and less than 10 events. 3 Only abstract available; little information provided. 4 Less than 50 patients in study.

Table 45: GRADE profile: what is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer? Comparison: sucralfate and steroid enema versus formalin

Quality assessment							Number of patients		Effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sucralfate + steroid**	**Formalin**	**Relative**	**95% CI**	**Absolute**	**Quality**
Bowel toxicity: rectal bleeding												
1	RCT	None	None	Serious[1]	Serious[2]	None	42 / 51 (82.4%)	33 / 51 (64.7%)	RR 1.27	(1.00 – 1.62)	175 more per 1,000 (from 0 more to 401 more)	LOW
Treatment-related morbidity												
1	RCT	None	None	Serious[1]	Serious[2]	None	Not reported	Not reported	Not reported	Not reported	Not pooled	LOW
Colostomy rate												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Patients underwent radiotherapy for carcinoma of the cervix. 2 Only 102 patients included in the study.

Update 2014

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. Whilst there were potential cost implications of making recommendations in this area, the lack of published analyses made it difficult to assess the feasibility of modelling this question. In addition, 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 men with signs or symptoms of radiation-induced enteropathy are offered care from a team of professionals with expertise in radiation-induced enteropathy (who may include oncologists, gastroenterologists, bowel surgeons, dietitians and specialist nurses). [new 2014]** **The nature and treatment of radiation-induced enteropathy should be included in the training programmes for oncologists and gastroenterologists. [2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of bowel toxicity, treatment-related morbidity, colostomy rate and health-related quality of life to be the most relevant to identifying the most effective interventions for treating the late effects of radiation-induced bowel toxicity. The outcome of bowel toxicity was reported for six of the interventions of interest. The outcome of health-related quality of life was reported for five of the interventions of interest. The outcome of treatment-related morbidity was reported for only one of the interventions of interest. The outcome of colostomy rate was not reported by the evidence.
Quality of the evidence	The evidence for bowel toxicity ranged from very low to moderate quality, as assessed by GRADE. For health-related quality of life the evidence ranged from very low to high quality and for treatment-related morbidity the evidence was very low quality. The GDG noted that the evidence came from a limited number of studies, several of which had small sample sizes. It was also noted that some of the studies included patients who had received radiotherapy for cancers other than prostate cancer and that several of the studies had investigated the acute effects of radiation induced bowel toxicity, rather than the late effects.
Trade-off between clinical benefits and harms	The GDG agreed that the variable quality of the evidence along with the fact that different outcomes were reported for different interventions made it difficult to determine if any interventions were effective in treating radiation-induced bowel toxicity. Given this uncertainty the GDG did not feel able to recommend any particular intervention but equally did not feel able to recommend that the use of any interventions be discontinued. The GDG therefore agreed to make recommendations for further research on the prevention and management of late effects of radiation on bowel function. The GDG noted, that men with radiation-induced bowel toxicity can present to a variety of different healthcare professionals, and so education and training in this area may lead to improved identification and treatment of these late effects. The GDG therefore agreed that training programmes for oncologists and gastroenterologists should include the nature and treatment of radiation-induced injury to the gastrointestinal tract. Despite not being able to make a recommendation for a particular

Update 2014

	intervention, the GDG considered that some guidance was needed on how to manage bowel toxicity in men who have had radical radiotherapy for prostate cancer as practice is currently variable. Based on their clinical experience, the GDG agreed that a multidisciplinary approach would be the best way to determine the most appropriate treatment, given the breadth of different interventions available. They therefore recommended that these men should have access to multidisciplinary professionals with expertise in the management of radiation-induced bowel toxicity.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. It was the opinion of the GDG that discussion between multidisciplinary professionals was unlikely to incur additional costs and that this discussion may lead to men having more effective treatments, thereby reducing costs. The GDG also agreed that it was unlikely there would be any additional costs from re-designing the curriculum for oncologists and gastroenterologists to include radiation-induced injury to the GI tract.

Research recommendation	**An interventional study should be conducted comparing drugs modifying the pathophysiology of post radiation changes in the bowel with placebo in men who have received radical radiotherapy for prostate cancer. Outcomes of interest are incidence of late bowel effects (e.g. bleeding, stricture, ulceration), and health-related quality of life. [2014]**
Why is this important	The pathophysiology of late radiation induced enteropathy is well documented, but there is lack of evidence on any therapies which can modify or prevent these late effects, as most therapeutic interventions currently utilised are symptomatic rather than prophylactic

Update 2014

4.5.122 Radiation-induced bowel cancer

Radiation can induce cancer as a late complication of radiotherapy, usually many years after treatment, but faecal occult blood testing is a poor discriminator due to telangiectasis.

The previous guideline advocated sigmoidoscopic surveillance for colorectal tumours after pelvic irradiation for prostate cancer.. Despite this, practice is still variable and questions have been raised about the diagnostic utility of sigmoidoscopy in this setting.

Clinical question: What is the diagnostic yield of screening sigmoidoscopy in the detection of radiation induced bowel cancer?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all pre-specified outcomes is summarised in Table 46. The incidence of bowel cancer following radiotherapy for prostate cancer was also collated from the literature.

Rectal bleeding

Four observational studies provided very low quality evidence of an overall prevalence of rectal bleeding in men screened using sigmoidoscopy following radiotherapy for prostate cancer of 27% (ranging from 20% to 50% in individual studies).

Malignancy

Very low quality evidence from a cohort study (Bolin *et al*. 2001) suggests malignancy may be found in around 3% of asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer. Screening was performed 16 months following radiotherapy.

Polyps

Very low quality evidence from two observational studies (Bolin *et al*. 2001; Wachter *et al*. 2000) suggest that polyps may occur in 21% (20% and 23% in each of the studies) of asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer.

Stricture

One cohort study (O'Brien *et al*. 2004) provided very low quality evidence on the absence of stricture in asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer, finding none in any of 20 men screened.

Hemorrhoidal nodes

One cohort study (Wachter *et al*. 2000) provided very low quality evidence on the presence of hemorrhoidal nodes in asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer. The study found a prevalence of 48% (21 cases in 44 men screened).

Ulceration

Very low quality evidence from two observational studies (Goldner *et al*. 2007; Wachter *et al*. 2000) suggests the presence of ulceration in asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer. Both studies found microulcerations in the distal anterior rectum wall. When combined, the studies estimate a prevalence of 2% (with rates of 1% and 5% individually). A third observational study (O'Brien *et al*. 2004) found no evidence of ulceration in any of 20 asymptomatic men screened following radiotherapy for prostate cancer.

Telangiectasia

Four observational studies provided very low quality evidence on the presence of telangiectasia in asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer. Combined these studies suggest a prevalence of telangiectasia of 57% and multiple telangiectases of 39% (individual studies ranged from 43% to 80% and 25% to 60% respectively).

Congested mucosa

Very low quality evidence from two cohort studies (Goldner *et al*. 2007; Wachter *et al*. 2000) suggests a prevalence of congested mucosa of 43% (range of 39% to 57% in individual studies) in asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer. Grade 1 congested mucosa (focal reddening of the mucosa with oedematous mucosa) was found in 15% to 32% of men; grade 2 (diffuse, not confluent, reddening of the mucosa with edematous mucosa) in 16% to 30%; and grade 3 (diffuse, confluent, reddening of the mucosa with edematous mucosa) in 8% to 13% of men in these studies.

Update 2014

Diagnostic yield, overall survival, sepsis, perforation, and health-related quality of life

These outcomes were not reported by any of the included studies.

Incidence of bowel cancer who have received radiotherapy for prostate cancer

Observational studies suggest a geometric mean raw incidence of 1.3% (range 0.1% to 6.6%) for the development of any secondary bowel cancer in men who have received radiotherapy for prostate cancer. Observational studies which report rates of secondary colon or rectal cancer in men who have received radiotherapy for prostate cancer suggest geometric mean raw incidences of 1.1% (range 0.4% to 3.4%) and 0.5% (range 0.0% to 8.3%) respectively. The meta-analysis included six studies and found a significantly higher risk of developing colorectal cancer following radiotherapy compared with no radiotherapy in men previously diagnosed with prostate cancer (RR 1.27 95% CI 1.23-1.31). The risk was also significantly higher for colon and rectal cancers individually (RR 1.09 95% CI 1.05-1.13 and RR 1.15 95% CI 1.10-1.21 respectively). However, there was wide variability between studies.

Six of the studies specifically looked at the increased risk of bowel cancer in those who had received EBRT alone for prostate cancer. There was no significant difference in the risk of any colorectal cancer or specifically colon cancer in those treated with EBRT compared to no radiotherapy ($p \geq 0.1$). However, there was still a significantly increased risk of rectal cancer following EBRT when compared with no radiotherapy (RR 1.21 95% CI 1.11-1.32).

Update 2014

In many of the studies a latency period was used to exclude the possibility of synchronous colorectal cancers, which varied considerably in length between studies. The exclusion of any studies which included secondary bowel cancers occurring within 5 years of diagnosis or treatment resulted in no significant increase in risk of any colorectal or colon cancer following radiotherapy ($p \geq 0.1$), but a significant increase in risk of rectal cancer for those treated with radiotherapy (RR 1.18 95% CI 1.07-1.31).

Only one observational study (Rapiti *et al*. 2008) allowed calculation of the incidence rate per person-year for any secondary bowel cancer in men who have received radiotherapy for prostate cancer; this was found to be 1,169 cases/100,000 person-years. The geometric mean incidence rates for colon and rectal cancer were found to be 220 cases/100,000 person-years (range 188 and 248 cases/100,000 person-years) and 102 cases/100,000 person-years (range 52 and 220 cases/100,000 person-years) respectively. This compares to 190 and 105 cases/100,000 person-years in the no-radiotherapy control groups respectively. From these figures, if 1,000 men were screened for 10 years we might expect to detect around 32 colorectal cancers in those undergoing radiotherapy, compared to around 30 colorectal cancers in those not undergoing radiotherapy.

Table 46: GRADE profile: what is the diagnostic yield of screening sigmoidoscopy in the detection of radiation-induced bowel cancer?

Quality assessment							No of cases / patients		Effect		
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sigmoidoscopy	No sigmoidoscopy	Relative (95% CI)	Absolute	Quality
Overall survival											
0	-	-	-	-	-	None	-	-	-	-	-
Perforation											
0	-	-	-	-	-	None	-	-	-	-	-
Sepsis											
0	-	-	-	-	-	None	-	-	-	-	-
Quality of life											
0	-	-	-	-	-	None	-	-	-	-	-
Malignancy											
1[1]	Cohort study	Serious	No serious inconsistency	No serious indirectness	Serious	None	7 / 277 (2.5%)	-	-	-	VERY LOW
Polyps											
2[2]	Cohort & diagnostic studies	No serious risk	No serious inconsistency	No serious indirectness	Serious	None	66 / 321 (20.6%)	-	-	-	VERY LOW
Stricture											
1	Cohort study	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	0 / 20 (0.0%)	-	-	-	VERY LOW
Hemorrhoidal nodes											
1	Cohort study	No serious risk	No serious inconsistency	No serious indirectness	Serious	None	21 / 44 (47.7%)	-	-	-	VERY LOW

Quality assessment							No of cases / patients		Effect		
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sigmoidoscopy**	**No sigmoidoscopy**	**Relative (95% CI)**	**Absolute**	**Quality**
Ulceration											
3	Cohort & diagnostic studies	No serious risk	Serious	No serious indirectness	Serious	None	4 / 230 (1.7%)	-	-	-	VERY LOW
Talengiectasia											
3	Cohort & diagnostic studies	No serious risk	Serious	No serious indirectness	Serious	None	130 / 230 (56.5%)	-	-	-	VERY LOW
Multiple talengiectases											
4	Cohort & diagnostic studies	No serious risk	Serious	No serious indirectness	Serious	None	100 / 258 (38.8%)	-	-	-	VERY LOW
Congested mucosa											
2[2]	Cohort study	No serious risk	Serious	No serious indirectness	Serious	None	91 / 210 (43.3%)	-	-	-	VERY LOW
Rectal bleeding											
4[2]	Cohort & diagnostic studies	No serious risk	Serious	No serious indirectness	Serious	None	70 / 258 (27.1%)	-	-	-	VERY LOW

1 *1 Only abstracts available. 2 Includes one study which is only available in abstract form. *Patients not reported to have any symptoms by articles*

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. No further economic modelling was undertaken because determining the diagnostic yield of sigmoidoscopy was a clinical issue and therefore not appropriate for modelling.

Recommendations	**Tell men that there is a small increase in the risk of colorectal cancer after radical external beam radiotherapy for prostate cancer. [new 2014]** **Carry out full investigations, including flexible sigmoidoscopy, in men who have symptoms of radiation-induced enteropathy to exclude inflammatory bowel disease or malignancy of the large bowel and to ascertain the nature of the radiation injury. Use caution when performing anterior wall rectal biopsy after brachytherapy because of the risk of fistulation. [2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of overall survival, sepsis, perforation, health-related quality of life, diagnostic yield for bowel cancer, diagnostic yield for other non-malignant pathology and bleeding to be the most important to determining the effectiveness of sigmoidoscopy in detecting second bowel malignancy after radical radiotherapy for prostate cancer. The outcomes of overall survival, sepsis, perforation and health-related quality of life were not reported in the evidence.
Quality of the evidence	The evidence for all reported outcomes was assessed by GRADE as very low quality. The GDG noted that the evidence came from a limited number of studies, some of which had small sample sizes. It was also noted that some of the evidence was only available in abstract form.
Trade-off between clinical benefits and harms	The GDG acknowledged that the evidence had shown men who had received radical radiotherapy for prostate cancer were at increased risk of developing secondary bowel malignancy, although the magnitude of this increase risk was uncertain. Since radiotherapy is only one of several potential treatment options for prostate cancer, the GDG agreed it was important to ensure men were given this information to assist them in making informed decisions about what treatment to have. The GDG noted that there was no evidence that flexible sigmoidoscopy increased the diagnostic yield of secondary bowel malignancy in men who had received radical radiotherapy for prostate cancer, compared to those men who had not . The GDG were also aware that the recommendation from CG58 that men treated with radical radiotherapy for prostate cancer be offered flexible sigmoidoscopy every 5 years had not been widely implemented. The GDG therefore agreed to delete this recommendation. The GDG noted that the available evidence did not contradict the recommendation from CG58 that men with symptoms of radiation-induced enteropathy should be investigated to exclude inflammatory bowel disease or malignancy of the large bowel and to ascertain the nature of the radiation injury. They therefore agreed to retain this recommendation because the GDG did not want patients to assume that symptoms were simply related to radiotherapy late effects. The GDG also agreed it was important to retain the recommendation from CG58 that caution should be exercised with anterior wall rectal biopsy following brachytherapy because of the risk of perforation.

Update 2014

Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG considered there would be no additional costs associated with informing patients of the increased risk of cancer, but potential cost savings from removing the recommendation to perform regular flexible sigmoidoscopy.

Update 2014

Research recommendation	**Research into the causes, and clinical trials of prevention and management of radiation-induced enteropathy should be undertaken [2008].**
Why is this important	There is little evidence on the factors that cause radiation-induced enteropathy, and how it can be prevented. There is also a lack of consensus on the optimal ways to detect radiation-induced enteropathy, on how to objectively assess its severity and on how to manage the symptoms caused by it.

4.5.2 Sexual dysfunction

Sexual dysfunction is a very common side effect of all treatments for localised prostate cancer. Sexual dysfunction is a general term which includes loss of libido, erectile dysfunction, loss of ejaculatory function, infertility and psychosexual issues.

The risk of loss of sexual function has an important influence on the decisions which men and their partners make about treatment for prostate cancer. Although there is evidence that, following an initial loss of erectile function, spontaneous improvements will occur in a proportion of men without specific intervention, most men who undergo radical treatment for prostate cancer experience erectile dysfunction and this is a cause of distress for the majority (see Chapter 2).

Recommendation	**Prior to radical treatment, warn men and, if they wish, their partner, that radical treatment for prostate cancer will result in an alteration of sexual experience, and may result in loss of sexual function. [2008, amended 2014]**
Qualifying statement	There is evidence from case series and GDG consensus to support this recommendation.
Recommendation	**Warn men and, if they wish, their partner, about the potential loss of ejaculation and fertility associated with radical treatment for prostate cancer. Offer sperm storage. [2008, amended 2014]**
Qualifying statement	There is evidence from case series and strong GDG consensus to support making this recommendation.
Recommendation	**Ensure that men have early and ongoing access to specialist erectile dysfunction services. [2008, amended 2014]**
Qualifying statement	There was GDG consensus to support making this recommendation.
Recommendation	**Offer men with prostate cancer who experience loss of erectile function phosphodiesterase type 5 (PDE5) inhibitors to improve their chance of spontaneous erections. [2008]**
Qualifying statement	Evidence from randomised trials has shown a clinical benefit for intervention with PDE5 inhibitors.
Recommendation	**If PDE5 inhibitors fail to restore erectile function or are contraindicated, offer men vacuum devices, intraurethral inserts or penile injections, or penile prostheses as an alternative. [2008]**
Qualifying statement	This recommendation is based on evidence from observational studies.

Clinical evidence (2008)

There is good evidence, from placebo controlled randomised trials, that PDE5 inhibitors can improve erectile function in men with erectile dysfunction after radical treatment for prostate cancer. Sildenafil (Incrocci *et al*. 2001) and tadalafil (Incrocci *et al*. 2006) have shown effectiveness for the treatment of erectile dysfunction after external beam radiotherapy. Sildenafil (Carson *et al*. 2002), tadalafil (Montorsi *et al*. 2004) and vardenafil (Brock *et al*. 2003) have shown effectiveness for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. The literature search did not find any trials directly comparing different PDE5 inhibitors in men with prostate cancer.

In a cohort study (Stephenson *et al*. 2005) and a large case series (Schover *et al*. 2002) of men after treatment for localised prostate cancer about half had tried treatment for erectile dysfunction. Sildenafil was the most widely used treatment. Invasive treatments (penile prostheses, penile injection) tended to be more effective but were less widely used; psychosexual counseling was the least effective.

A meta-analysis of placebo controlled trials in patients with erectile dysfunction of mixed aetiology concluded prostaglandin E1 was beneficial (Urciuoli *et al*. 2004). Three RCTs examined psychosexual counseling in men with prostate cancer (Canada *et al*. 2005; Giesler *et al*. 2005; Lepore *et al*. 2003), but none showed an improvement in sexual function.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Research recommendation	**Further research should be conducted into the timing and effectiveness of treatments for erectile dysfunction after all treatments for prostate cancer. [2008]**
Why is this important	The 3 most commonly used treatments for prostate cancer, surgery, radiotherapy and androgen deprivation therapy, all cause erectile dysfunction. There has been research into treatments following surgery but the trials are not of high quality. Very little research has been undertaken in men treated with radiotherapy or androgen deprivation therapy. Erectile dysfunction is one of the top 3 treatment related morbidities reported by men with prostate cancer.

4.5.3 Urinary incontinence

Urinary incontinence of all types has been reported after prostate cancer treatment. Radical prostatectomy can especially lead to stress incontinence, which may be temporary or permanent. Incontinence may be a problem after brachytherapy and external beam radiotherapy, in those men who have also had a trans-urethral resection of the prostate. The severity of the symptoms is very variable as is the degree to which this bothers individual men. Treatments for incontinence include physical (pelvic floor muscle re-education, bladder retraining), medical (drug therapy) or surgical (injection of bulking agents, artificial urinary sphincters or perineal sling).

Recommendation	**Offer men experiencing troublesome urinary symptoms before treatment a urological assessment. [2008]** **Warn men undergoing radical treatment for prostate cancer of the likely effects of the treatment on their urinary function. [2008]**
Qualifying statement	There was case series evidence supported by GDG consensus that these

	recommendations should be made.
Recommendation	**Ensure that men with troublesome urinary symptoms after treatment have access to specialist continence services for assessment, diagnosis and conservative treatment. This may include coping strategies, along with pelvic floor muscle re-education, bladder retraining and pharmacotherapy. [2008]** **Refer men with intractable stress incontinence to a specialist surgeon for consideration of an artificial urinary sphincter. [2008]**
Qualifying statement	There was strong GDG consensus and evidence from randomised trials to support making these recommendations
Recommendation	**Do not offer injection of bulking agents into the distal urinary sphincter to treat stress incontinence. [2008]**
Qualifying statement	The evidence from one small randomised trial did not support the use of this intervention.

Clinical evidence (2008)

Pelvic floor re-education

Systematic reviews of RCTs of pelvic floor muscle exercise (PME) training in men (Dorey 2005; Hunter *et al*. 2004) suggest that PME training using biofeedback is associated with earlier return to continence after radical prostatectomy. Continence rates at one year post prostatectomy, however, were similar in PME and non-PME groups. Two good quality RCTs published since the reviews (Burgio *et al*. 2006; Filocamo *et al*. 2005) showed a benefit of early PMEs for post-prostatectomy incontinence.

The systematic reviews (Dorey 2005; Hunter *et al*. 2004) concluded that there was insufficient evidence to support enhancements (such as biofeedback and electrical or magnetic stimulation) to PMEs. A RCT conducted since these systematic reviews (Yokoyama *et al*. 2004) showed earlier return to post radical prostatectomy continence in men treated using external electrical or magnetic stimulation of the pelvic floor muscles than in those treated with PMEs.

Surgical treatment

A single small RCT (Imamoglu *et al*. 2005) compared injection of urethral bulking agent with the AMS 800 artificial urinary sphincter in the treatment of post radical prostatectomy urinary incontinence. In men with total incontinence after prostatectomy, the artificial urinary sphincter was more effective in terms of number of pads used and grams of urine lost. In men with minimal incontinence, however, there was no significant difference between the two treatments.

Cost-effectiveness evidence (2008)

The literature search on interventions for urinary incontinence identified 184 potentially relevant papers. Nine of these papers were read in full but none were appraised as they did not include any economic evaluations. No economic modelling was attempted because there was considered to be insufficient clinical information on which to base a model.

Research recommendation	**Further research is required into the causes, prevention and treatment strategies for urinary incontinence in men with prostate cancer. [2008]**

Why is this important	Urinary incontinence is the most commonly reported treatment related side effect after radical prostatectomy. It can also occur after other types of prostate surgery and radiotherapy. There are few comparative data on management of this distressing condition.

4.6 Follow-up

Routine follow-up after treatment of localised disease is used:

- to identify local recurrent disease at a stage when further radical treatment might be effective
- to identify and treat the complications of therapy
- to give information and address concerns
- to audit the outcomes of treatment.

Methods of monitoring disease control and detecting disease recurrence include physical examination, blood tests such as the PSA level, and imaging investigations. It is rare for local clinical relapse to be detected before the PSA rises from baseline values. The appropriate management of men with a rising PSA is an important area of clinical controversy, and will be considered in some detail (see Chapter 5).

The traditional model for follow-up has been based around regular out patient visits to hospital doctors. Alternative models include telephone follow-up, nurse-led clinics, and follow-up in primary care. Although follow-up needs to be long term, this does not necessarily need to be hospital-based.

Recommendation	**Discuss the purpose, duration, frequency and location of follow-up with each man with localised prostate cancer[l], and if he wishes, his partner or carers. [2008]** **Clearly advise men with prostate cancer about potential longer term adverse effects of treatment and when and how to report them. [2008]** **Men with prostate cancer who have chosen a watchful waiting regimen with no curative intent should normally be followed up in primary care in accordance with protocols agreed by the local urological cancer MDT and the relevant primary care organisation(s). Their PSA should be measured at least once a year. [2008]** **Check PSA levels for all men with prostate cancer who are having radical treatment at the earliest 6 weeks following treatment, at least every 6 months for the first 2 years and then at least once a year thereafter. [2008]** **Do not routinely offer DRE to men with localised prostate cancer while the PSA remains at baseline levels. [2008]** **After at least 2 years, offer follow-up outside hospital (for example, in primary care) by telephone or secure electronic communications to men with a stable PSA who have had no significant treatment complications, unless they are taking part in a clinical trial that requires formal clinic-based follow-up. Direct access to the urological cancer MDT should be offered and explained. [2008]**
Qualifying statement	In the absence of reliable evidence, these recommendations are based on GDG consensus.

l This may also apply to some men with locally advanced prostate cancer

Clinical evidence (2008)

Literature searches did not identify any studies comparing different follow-up frequencies. Some authors have recommended strategies for follow-up (Carroll *et al*. 2001; Catton *et al*. 2003; Edelman *et al*. 1997; Yao & DiPaola 2003) but none comes from a systematic review of the evidence. Studies of the acceptability of follow-up strategies in primary care have not reported rates of disease recurrence and survival (Rose *et al*.1996; Cathala *et al*. 2003; Booker *et al*. 2004).

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

4.7 References

2008

Albertsen, P. C., Hanley, J. A. & Fine, J. (2005) 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA, 293: 2095–2101.

Akakura, K., Suzuki, H., Ichikawa, T., Fujimoto, H., Maeda, O., Usami, M., Hirano, D., Takimoto, Y., Kamoto, T., Ogawa, O., Sumiyoshi, Y., Shimazaki, J. & Kakizoe, T. (2006) A Randomized Trial Comparing Radical Prostatectomy Plus Endocrine Therapy versus External Beam Radiotherapy Plus Endocrine Therapy for Locally Advanced Prostate Cancer: Results at Median Follow-up of 102 Months. Jpn.J Clin Oncol, 36: 789–793.

Beerlage HP, Thuroff, S., Debruyne, F. M., Chaussy, C. & de la Rosette, J. J. (1999) Transrectal high-intensity focused ultrasound using the Ablatherm device in the treatment of localized prostate carcinoma. Urology, 54: 273–277.

Bill-Axelson, A., Holmberg, L., Ruutu, M., Haggman, M., Andersson, S. O., Bratell, S., Spangberg, A., Busch, C., Nordling, S., Garmo, H., Palmgren, J., Adami, H. O., Norlen, B. J., Johansson, J. E., Scandinavian Prostate Cancer Group & 4. (2005) Radical prostatectomy versus watchful waiting in early prostate cancer.. N Engl J Med, 352: 1977–1984.

Booker, J., Eardley, A., Cowan, R., Logue, J., Wylie, J. & Caress, A. (2004) Telephone first post-intervention follow-up for men who have had radical radiotherapy to the prostate: evaluation of a novel service delivery approach. European Journal of Oncology Nursing; 8(4): 325–333.

Brock, G., Nehra, A., Lipshultz, L. I., Karlin, G. S., Gleave, M., Seger, M. & Padma-Nathan, H. (2003) Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic prostatectomy. J Urol, 170: 1278–1283.

Burgio, K. L., Goode, P. S., Urban, D. A., Umlauf, M. G., Locher, J. L., Bueschen, A. & Redden, D. T. (2006) Preoperative biofeedback assisted behavioral training to decrease post-prostatectomy incontinence: A randomized, controlled trial. J Urol, 175: 196–201.

Buron C; Le Vue B; Cosset J-M; Pommier P; Peiffert D; Delannes M; Flam T; Guerief S; Salem N; Chauvenic L and Livartowski A. (2007) Brachytherapy versus prostatectomy in the localized prostate cancer: results of a French multicenter prospective medico-economic study. International Journal of Radiation Oncology, Biology, Physics 67(3): 812–822.

Calvert, N.W., *et al*., (2003) Effectiveness and cost-effectiveness of prognostic markers in prostate cancer. British Journal of Cancer 88(1): 31–35.

Canada, A. L., Neese, L. E., Sui, D. & Schover, L. R. (2005) Pilot intervention to enhance sexual rehabilitation for couples after treat- ment for localized prostate carcinoma. Cancer, 104: 2689–2700.

Carroll, P., Coley, C., McLeod, D., Schellhammer, P., Sweat, G., Wasson, J., Zietman, A. & Thompson, I. (2001) Prostate-specific anti- gen best practice policy--part II: prostate cancer staging and post-treatment follow-up. [Review] [38 refs]. Urology, 57: 225–229.

Carson, C. C., Burnett, A. L., Levine, L. A. & Nehra, A. (2002) The efficacy of sildenafil citrate (Viagra((R))) in clinical populations: An update. Urology, 60: 12–27.

Cathala, N., Brillat, F., Mombet, A., Lobel, E., Prapotnich, D., Alexandre, L. & Vallancien, G. (2003) Patient followup after radical prostatectomy by internet medical file. J Urol, 170: 2284–2287.

Catton, C., Milosevic, M., Warde, P., Bayley, A., Crook, J., Bristow, R. & Gospodarowicz, M. (2003) Recurrent prostate cancer following external beam radiotherapy: Follow-up strategies and management. Urol Clin North Am, 30: 751-+.

Chaussy, C. & Thuroff, S. (2003) The status of high-intensity focused ultrasound in the treatment of localized prostate cancer and the impact of a combined resection. Current Urology Reports, 4: 248–252.

Chin, J. L., Ng, C. K., Touma, N. J., Pus, N. J., Hardie, R., Abdelhady, M., Rodrigues, G., Radwan, J., Venkatesan, V., Moussa, M., Downey, D. B. & Bauman, G. (2007) Randomized trial comparing cryoablation and external beam radiotherapy for T2C-T3B prostate cancer. Prostate Cancer Prostatic Dis.

Dearnaley, D. P., Khoo, V. S., Norman, A. R., Meyer, L., Nahum, A., Tait, D., Yarnold, J. & Horwich, A. (1999) Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet, 353: 267–272.

Dearnaley, D. P., Hall, E., Lawrence, D., Huddart, R. A., Eeles, R., Nutting, C. M., Gadd, J., Warrington, A., Bidmead, M. & Horwich, A. (2005) Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. Br J Cancer, 92: 488–498.

Dearnaley, D. P., Sydes, M. R., Graham, J. D., Aird, E. G., Bottomley, D., Cowan, R. A., Huddart, R. A., Jose, C. C., Matthews, J. H., Millar, J., Moore, A. R., Morgan, R. C., Russell, J. M., Scrase, C. D., Stephens, R. J., Syndikus, I. & Parmar, M. K. (2007) Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncology, 8: 475–487.

Donnelly, B., Saliken, J., Brasher, P., Ernst, D., Lau, H., Rewcastle, J. & Trpkov, K. A Randomized Trial of External Beam Radiotherapy Versus Cryoablation in Patients with Localized Prostate Cancer. The American Urological Association Annual Meeting. Abstract 1141. 2007.

Dorey, G. (2005) Men's health. Restoring pelvic floor function in men: review of RCTs. Br J Nurs. 14(19): 1014 –1018.

Doust, Miller, Duchesne, Kitchener and Weller (2004). A systematic review of brachytherapy: is it an effective and safe treatment for localised prostate cancer. Australian Family Physician, vol. 33, no. 7 pp. 525–529.

Edelman, M. J., Meyers, F. J. & Siegel, D. (1997) The utility of follow-up testing after curative cancer therapy. A critical review and economic analysis. [Review] [133 refs]. J Gen Intern.Med, 12: 318–331.

Ficarra, V., Antoniolli, S. Z., Novara, G., Parisi, A., Fracalanza, S., Martignoni, G. & Artibani, W. (2006) Short-term outcome after high-intensity focused ultrasound in the treatment of patients with high-risk prostate cancer. BJU International, 98: 1193–1198.

Filocamo, M. T., Li, M., Del, P. G., Cecconi, F., Marzocco, M., Tosto, A. & Nicita, G. (2005) Effectiveness of early pelvic floor rehabilitation treatment for post-prostatectomy incontinence. Eur Urol, 48: 734 –738.

Ganzer, R., Rogenhofer, S., Walter, B., Lunz, J. C., Schostak, M., Wieland, W. F. & Blana, A. (2007) PSA Nadir Is a Significant Predictor of Treatment Failure after High-Intensity Focussed Ultrasound (HIFU) Treatment of Localised Prostate Cancer. Eur Urol.

Giesler, R. B., Given, B., Given, C. W., Rawl, S., Monahan, P., Burns, D., Azzouz, F., Reuille, K. M., Weinrich, S., Koch, M. & Champion, V. (2005) Improving the quality of life of patients with prostate carcinoma: a randomized trial testing the efficacy of a nurse-driven intervention. Cancer, 104: 752–762.

Gelet, A., Chapelon, J. Y., Bouvier, R., Pangaud, C. & Lasne, Y. (1999) Local control of prostate cancer by transrectal high intensity focused ultrasound therapy: Preliminary results. J Urol, 161: 156–162.

Gelet, A., Chapelon, J. Y., Bouvier, R., Rouviere, O., Lasne, Y., Lyonnet, D. & Dubernard, J. M. (2000) Transrectal high-intensity focused ultrasound: minimally invasive therapy of localized prostate cancer.[erratum appears in J Endourol 2000 Oct;14(8):697]. J Endourol., 14: 519–528.

Horwitz, E.M. Hanlon, AL (1999) The cost effectiveness of 3D conformal radiation therapy compared with conventional techniques for patients with clinically localized prostate cancer. International Journal of Radiation Oncology, Biology, Physics 45(5): 1219–1125.

Hummel, S., Paisley, S., Morgan, A., Currie, E. & Brewer, N. (2003) Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review. [Review] [175 refs]. Health Technology Assessment (Winchester, England), 7: iii-157.

Hunter, K. F., Moore, K. N., Cody, D. J. & Glazener, C. M. A. (2004) Conservative management for postprostatectomy urinary incontinence [Cochrane review]. 2004 ;(2): .

Incrocci, L., Slagter, C., Slob, A. K. & Hop, W. C. (2006) A randomized, double-blind, placebo-controlled, cross-over study to assess the efficacy of tadalafil (Cialis) in the treatment of erectile dysfunction following three-dimensional conformal external-beam radiotherapy for prostatic carcinoma. Int J Radiat.Oncol Biol.Phys., 66: 439–444.

Incrocci, L., Koper, P. C., Hop, W. C. & Slob, A. K. (2001) Sildenafil citrate (Viagra) and erectile dysfunction following external beam radiotherapy for prostate cancer: a randomized, double-blind, placebo-controlled, cross-over study. Int J Radiat.Oncol Biol.Phys., 51: 1190–1195.

Imamoglu, M. A., Tuygun, C., Bakirtas, H., Yigitbasi, O. & Kiper, A. (2005) The comparison of artificial urinary sphincter implantation and endourethral macroplastique injection for the treatment of postprostatectomy incontinence. Eur Urol, 47: 209–213.

Klotz, L 'A Phase III Study of Active Surveillance Therapy Against Radical Treatment in Patients Diagnosed with Favourable Risk Prostate Cancer [START]'[online]. Available from: http://www.cancer.gov/clinicaltrials/CAN-NCIC-CTG-PR11 [accessed 23 July 2007] Konski A *et al*. (2006) Using decision analysis to determine the cost-effectiveness of intensity-modulated radiation therapy in the treatment of intermediate risk prostate cancer. International Journal of Radiation Oncology, Biology, Physics 66(2): 408–415.

Koper, P. C., Jansen, P., van, P. W., van, O. M., Wijnmaalen, A. J., Lebesque, J. V. & Levendag, P. C. (2004) Gastro-intestinal and genito-urinary morbidity after 3D conformal radiotherapy of prostate cancer: observations of a randomized trial. Radiother.Oncol, 73: 1–9.

Lee, H. M., Hong, J. H. & Choi, H. Y. (2006) High-intensity focused ultrasound therapy for clinically localized prostate cancer. Prostate Cancer Prostatic Dis., 9: 439–443.

Lepore, S. J., Helgeson, V. S., Eton, D. T. & Schulz, R. (2003) Improving quality of life in men with prostate cancer: a randomized controlled trial of group education interventions. Health psychology : official journal of the Division.of Health Psychology, American Psychological Association, 22: 443–452.

Lukka, H., Hayter, C., Julian, J. A., Warde, P., Morris, W. J., Gospodarowicz, M., Levine, M., Sathya, J., Choo, R., Prichard, H., Brund- age, M. & Kwan, W. (2005) Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. J Clin Oncol, 23: 6132–6138.

Martin, R. M., Gunnell, D., Hamdy, F., Neal, D., Lane, A. & Donovan, J. (2006) Continuing controversy over monitoring men with localized prostate cancer: A systematic review of programs in the prostate specific antigen era. Journal of Urology, 176: 439–449.

Montorsi, F., Padma-Nathan, H., McCullough, A., Brock, G. B., Broderick, G., Ahuja, S., Whitaker, S., Hoover, A., Novack, D., Murphy, A. & Varanese, L. (2004) Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: A randomized, double-blind, placebo controlled trial. J Urol, 172: 1036–1041.

National Institute for Clinical Excellence (2002). Guidance on cancer services - improving outcomes in urological cancers. The manual. London: National Institute for Clinical Excellence.

National Institute for Health and Clinical Excellence (2005a) Cryotherapy as a primary treatment for prostate cancer. NICE Interventional Procedure Guidance 145. Available from www.nice.org.uk/IPG145

National Institute for Health and Clinical Excellence (2005b) Cryotherapy for recurrent prostate cancer. NICE interventional procedure guidance 119. Available from www.nice.org.uk/IPG119

National Institute for Health and Clinical Excellence (2005c) High-intensity focused ultrasound for prostate cancer. NICE interventional procedure guidance 118. Available from www.nice.org.uk/IPG118

Nilsson, S., Norlen, B. J. & Widmark, A. (2004) A systematic overview of radiation therapy effects in prostate cancer. [Review] [390 refs]. Acta Oncol, 43: 316–381.

Norderhaug, Dahl, Høisæter, Heikkilä, Klepp, Olsen, Kristiansen, Wæhre, Johansen. (2003) Brachytherapy for prostate cancer: A systematic Review of Clinical and Cost Effectiveness. European Urology, 44: 40–46

Paulson, D. F., Lin, G. H., Hinshaw, W. & Stephani, S. (1982) Radical surgery versus radiotherapy for adenocarcinoma of the prostate. J Urol, 128: 502–504.

Peeters, S. T., Heemsbergen, W. D., Koper, P. C., van Putten, W. L., Slot, A., Dielwart, M. F., Bonfrer, J. M., Incrocci, L. & Lebesque, J. V. (2006) Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol, 24: 1990–1996.

Poissonnier, L., Chapelon, J. Y., Rouviere, O., Curiel, L., Bouvier, R., Martin, X., Dubernard, J. M. & Gelet, A. (2007) Control of prostate cancer by transrectal HIFU in 227 patients. Eur Urol., 51: 381–387.

Poissonnier, L., Gelet, A., Chapelon, J. Y., Bouvier, R., Rouviere, O., Pangaud, C., Lyonnet, D. & Dubernard, J. M. (2003) [Results of trans- rectal focused ultrasound for the treatment of localized prostate cancer (120 patients with PSA < or + 10ng/ml]. Prog.Urol, 13: 60–72.

Pollack, A., Zagars, G. K., Starkschall, G., Antolak, J. A., Lee, J. J., Huang, E., Von Eschenbach, A. C., Kuban, D. A. & Rosen, I. (2002) Prostate cancer radiation dose response: Results of the M. D. Anderson phase III randomized trial. International Journal of Radiation Oncology Biology Physics, 53: 1097–1105.

Rose, M. A., Shrader-Bogen, C. L., Korlath, G., Priem, J. & Larson, L. R. (1996) Identifying patient symptoms after radiotherapy using a nurse-managed telephone interview. Oncol Nurs.Forum; 23(1):99–102.

Schover, L. R., Fouladi, R. T., Warneke, C. L., Neese, L., Klein, E. A., Zippe, C. & Kupelian, P. A. (2002) The use of treatments for erectile dysfunction among survivors of prostate carcinoma. Cancer, 95: 2397–2407.

Shelley, M., Wilt, T., Coles, B. & Mason, M. (2007) Cyrotherapy for localised prostate cancer. Cochrane Database Syst Rev., CD005010

Steineck, G., Helgesen, F., Adolfsson, J., Dickman, P. W., Johansson, J. E., Norlen, B. J., Holmberg, L. & Scandinavian Prostatic Cancer

Group (2002) Quality of life after radical prostatectomy or watchful waiting. N Engl J Med, 347: 790–796.

Stephenson, R. A., Mori, M., Hsieh, Y. C., Beer, T. M., Stanford, J. L., Gilliland, F. D., Hoffman, R. M. & Potosky, A. L. (2005) Treatment of erectile dysfunction following therapy for clinically localized prostate cancer: patient reported use and outcomes from the Surveillance, Epidemiology, and End Results Prostate Cancer Outcomes Study. J Urol, 174: 646–650.

Thuroff, S., Chaussy, C., Vallancien, G., Wieland, W., Kiel, H. J., Le, D. A., Desgrandchamps, F., de la Rosette, J. J. & Gelet, A. (2003) High-intensity focused ultrasound and localized prostate cancer: efficacy results from the European multicentric study. J Endourol., 17: 673–677.

Uchida, T., Ohkusa, H., Yamashita, H., Shoji, S., Nagata, Y., Hyodo, T. & Satoh, T. (2006) Five years experience of transrectal high- intensity focused ultrasound using the Sonablate device in the treatment of localized prostate cancer. Int J Urol., 13: 228–233.

Uchida, T., Baba, S., Irie, A., Soh, S., Masumori, N., Tsukamoto, T., Nakatsu, H., Fujimoto, H., Kakizoe, T., Ueda, T., Ichikawa, T., Ohta, N., Kitamura, T., Sumitomo, M., Hayakawa, M., Aoyagi, T., Tachibana, M., Ikeda, R., Suzuki, K., Tsuru, N., Suzuki, K., Ozono, S., Fujimoto, K., Hirao, Y., Monden, K., Nasu, Y., Kumon, H., Nishi, K., Ueda, S., Koga, H. & Naitoh, S. (2005) Transrectal high- intensity focused ultrasound in the treatment of localized prostate cancer: a multicenter study. Hinyokika Kiyo - Acta Urologica Japon- ica, 51: 651–658.

Uchida, T., Sanghvi, N. T., Gardner, T. A., Koch, M. O., Ishii, D., Minei, S., Satoh, T., Hyodo, T., Irie, A. & Baba, S. (2002) Transrectal high-intensity focused ultrasound for treatment of patients with stage T1b-2n0m0 localized prostate cancer: a preliminary report. Urology, 59: 394–398.

Urciuoli, R., Cantisani, T. A., CarliniI, M., Giuglietti, M. & Botti, F. M. (2004) Prostaglandin E1 for treatment of erectile dysfunction [Cochrane review].(2).

Yao, S. L. & DiPaola, R. S. (2003) An evidence-based approach to prostate cancer follow-up. [Review] [56 refs]. Semin.Oncol, 30: 390–400.

Yeoh, E. E. K., Fraser, R. J., McGowan, R. E., Botten, R. J., Di Matteo, A. C., Roos, D. E., Penniment, M. G. & Borg, M. F. (2003) Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: Early results of a Phase III randomized trial. Int J Radiat.Oncol Biol.Phys., 55: 943–955.

Yokoyama, T., Nishiguchi, J., Watanabe, T., Nose, H., Nozaki, K., Fujita, O., Inoue, M. & Kumon, H. (2004) Comparative study of effects of extracorporeal magnetic innervation versus electrical stimulation for urinary incontinence after radical prostatectomy. Urology, 63: 264–267.

2014

Arregui Lopez E, Bueno Serrano C, Quintana Navarro G, *et al*. (2012). Steady diet as prophylaxis of acute diarrhea in preoperative pelvic radiotherapy of rectal adenocarcinoma. Radiotherapy and Oncology Conference(var.pagings): S109

Asimakopoulos AD, Pereira Fraga CT, Annino F, *et al*. (2011). Randomized comparison between laparoscopic and robot-assisted nerve-sparing radical prostatectomy. Journal of Sexual Medicine 8(5): 1503-1512.

Ball AJ, Gambill B, Fabrizio MD, *et al*. (2006). Prospective longitudinal comparative study of early health-related quality-of-life outcomes in patients undergoing surgical treatment for localized prostate cancer: a short-term evaluation of five approaches from a single institution. J Endourol 20: 723–31.

Bannuru RR, Dvorak T, Obadan N, *et al*. (2011). Comparative evaluation of radiation treatments for clinically localized prostate cancer: an updated systematic review. Annals of Internal Medicine 155: 171-178.

Berge V, Berg RE, Hoff JR, *et al*. (2013). A prospective study of transition from laparoscopic to robot-assisted radical prostatectomy: quality of life outcomes after 36-month follow-up. Urology 81(4): 781-786.

Bolin TD, Kneebone A, and Larsson T (2001). Sigmoidoscopic findings following radiation for prostate cancer. Gastroenterology 120(5): A284-A284.

Botten RJ, DiMatteo AC, Butters J, *et al*. (2011). Randomised Trial of Argon Plasma Coagulation (APC) Therapy Verses Topical Formalin for Persistent Rectal Bleeding and Anorectal Dysfunction After Radiation Therapy (RT) for Carcinoma of the Prostate (CAP). Gastroenterology 140, S796.

Bye A, Kaasa S, Ose T, *et al*. (1992). The influence of low fat, low lactose diet on diarrhoea during pelvic radiotherapy. Clinical Nutrition 11, 147-153.

Capirci C, Polico C, Amichetti M, *et al*. (2000). Diet prevention of radiation acute enteric toxicity: multicentric randomized study. Radiotherapy and Oncology 56 (Suppl 1): S44

Chruscielewska-Kiliszek MR, Regula J, Polkowski M, *et al*. (2013). Sucralfate or placebo following argon plasma coagulation for chronic radiation proctitis: a randomized double blind trial. Colorectal Disease 15(1): e48-e55.

Clarke RE, Tenorio LM, Hussey JR, *et al*. (2008). Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. International Journal of Radiation Oncology, Biology, Physics 72: 134-143.

Curtis, L. Unit Costs of Health and Social Care 2012, Personal Social Services Research Unit (PSSRU), University of Kent, Canterbury (2010).

da Silva Franca CA, Vieira SL, Carvalho AC, *et al*. (2010). Localized prostate cancer with intermediate- or high-risk features treated with combined external beam radiotherapy and iodine-125 seed brachytherapy. Brachytherapy 9: 307-312.

Dahabreh IJ, Chung M, Balk EM, *et al*. (2012). Active surveillance in men with localized prostate cancer: a systematic review. Ann Intern Med. 156(8): 582-90.

Delia P, Sansotta G, Donato V, *et al*. (2007). Use of probiotics for prevention of radiation-induced diarrhea. World journal of gastroenterology: WJG 13: 912-915.

Update 2014

Drouin SJ, Vaessen C, Hupertan V, *et al*. (2009). Comparison of mid-term carcinologic control obtained after open, laparoscopic, and robot-assisted radical prostatectomy for localized prostate cancer. World J Urol 27: 599–605.

Fiori CM (2005). Pure versus robot-assisted laparoscopic prostatectomy: Single centre, single surgeon experience. Journal of Urology Conference(var.pagings): e458.

Fuccio L, Guido A, Eusebi LH, *et al*. (2009). Effects of probiotics for the prevention and treatment of radiation-induced diarrhea - DARE structured abstract available. Journal of Clinical Gastroenterology 43: 506-513.

Fuccio L, Guido A, Laterza L, *et al*. (2011). Randomised clinical trial: preventive treatment with topical rectal beclomethasone dipropionate reduces post-radiation risk of bleeding in patients irradiated for prostate cancer. Alimentary pharmacology & therapeutics 34: 628-637.

Germain I, Desjardins J, Demers M, *et al*. (2011). Phase III study: Impact of probiotics on diarrhea in patients treated with pelvic radiation. International Journal of Radiation Oncology Biology Physics Conference 2-S668.

Giralt J, Regadera JP, Verges R, *et al*. (2008). Effects of probiotic Lactobacillus casei DN-114 001 in prevention of radiation-induced diarrhea: results from multicenter, randomized, placebo-controlled nutritional trial. International Journal of Radiation Oncology, Biology, Physics 71: 1213-1219.

Goldner G, Tomicek B, Becker G, *et al*. (2007). Proctitis after external-beam radiotherapy for prostate cancer classified by Vienna Rectoscopy Score and correlated with EORTC/RTOG score for late rectal toxicity: results of a prospective multicenter study of 166 patients. International Journal of Radiation Oncology, Biology, Physics 67(1): 78-83.

Hohwu L. "A short-term cost-effectiveness study comparing robot-assisted laparoscopic and open retropubic radical prostatectomy." Journal of Medical Economics 14.4 (2011): 403-09.

Hoskin PJ, Rojas AM, Ostler PJ, *et al*. (2013). Quality of life after radical radiotherapy for prostate cancer: longitudinal study from a randomised trial of external beam radiotherapy alone or in combination with high dose rate brachytherapy. Clinical Oncology 25: 321-327.

Hoskin PJ, Motohashi K, Bownes P, *et al*. (2007). High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology 84: 114-120.

Hoskin, P. J., Rojas, A. M., Bownes, P. J., Lowe, G. J., Ostler, P. J. & Bryant, L. (2012) Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiotherapy & Oncology, 103: 217-222.

Hoskin, P. J., Motohashi, K., Bownes, P., Bryant, L. & Ostler, P. (2007) High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology, 84: 114-120.

Hovdenak N, Sorbye H, and Dahl O. (2005). Sucralfate does not ameliorate acute radiation proctitis: randomised study and meta-analysis. Clinical Oncology 17: 485-491.

Joint Formulary Committee. British National Formulary (online ed. 65) London: BMJ Group and Pharmaceutical Press <http://www.bnf.org>

Joseph JV, Vicente I, Madeb R, *et al*. (2005). Robot-assisted vs pure laparoscopic radical prostatectomy: are there any differences? BJU Int 96: 39–42.

Update 2014

Kapur G, Windsor PM, and McCowan C. (2010). The effect of aerobic exercise on treatment-related acute toxicity in men receiving radical external beam radiotherapy for localised prostate cancer. European journal of cancer care 19: 643-647.

Khatami A, Aus G, Damber JE, *et al*. (2007). PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. International Journal of Cancer 120(1): 170-174.

Khatami A, Hugosson J, Wang W, *et al*. (2009). Ki-67 in screen-detected, low-grade, low-stage prostate cancer, relation to prostate-specific antigen doubling time, Gleason score and prostate-specific antigen relapse after radical prostatectomy. Scandinavian Journal of Urology & Nephrology 43(1): 12-18.

Klotz L, Zhang L, Lam A, *et al*. (2010). Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. Journal of Clinical Oncology 28(1): 126-131.

Kochhar R, Patel F, Dhar A, *et al*. (1991). Radiation induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalzine plus rectal steroids versus rectal sucralfate. Digestive Diseases and Sciences 36(1): 103-107.

Korfage IJ, Essink-Bot ML, Borsboom GJ, Madalinska JB, Kirkels WJ, Habbema JD *et al*. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Int J Cancer 2005;116:291-6.

Lord J, Willis S, Eatock J, Tappenden P, Trapero-Bertran M, Miners A, Crossan C, Westby M, Anagnostou A, Taylor S, Mavranezouli I, Wonderling D, Alderson P, Ruiz F. Economic modelling of diagnostic and treatment pathways in NICE clinical guidelines: the MAPGuide project. Under review

Magheli A, Gonzalgo ML, Su LM, *et al*. (2011). Impact of surgical technique (open vs laparoscopic vs robotic-assisted) on pathological and biochemical outcomes following radical prostatectomy: an analysis using propensity score matching. BJU International 107(12): 1956-1962.

Malcolm JB, Fabrizio MD, Barone BB, *et al*. (2010). Quality of life after open or robotic prostatectomy, cryoablation or brachytherapy for localized prostate cancer. J Urol 183: 1822–8.

Merrick GS, Wallner KE, Butler WM, *et al*. (2012). 20 Gy versus 44 Gy of supplemental external beam radiotherapy with palladium-103 for patients with greater risk disease: results of a prospective randomized trial. International Journal of Radiation Oncology, Biology, Physics 82: e449-e455.

Miller J, Smith A, Kouba E, *et al*. (2007). Prospective evaluation of short-term impact and recovery of health related quality of life in men undergoing robotic assisted laparoscopic radical prostatectomy versus open radical prostatectomy. J Urol 178: 854–8.

Mirza M, Art K, Wineland L, *et al*. (2011). A comparison of radical perineal, radical retropubic, and robot-assisted laparoscopic prostatectomies in a single surgeon series. Prostate Cancer Article Number: 878323

Nelamangala R, Javali TD, Dharanipragada K, *et al* (2012). Formalin dab, the effective way of treating haemorrhagic radiation proctitis: a randomized trial from a tertiary care hospital in South India. Colorectal disease 14(7): 876-882.

NHS reference costs 2011-12 [database on the Internet]. London: UK Department of Health; [accessed March 2013].

Update 2014

O'Brien PC, Hamilton CS, Denham JW, *et al*. (2004). Spontaneous improvement in late rectal mucosal changes after radiotherapy for prostate cancer. International Journal of Radiation Oncology, Biology, Physics 58(1): 75-80.

Pilepich MV, Paulus R, St Clair W, *et al*. (2006). Phase III study of pentosanpolysulfate (PPS) in treatment of gastrointestinal tract sequelae of radiotherapy. American Journal of Clinical Oncology 29: 132-137.

Pieters BR, de Back DZ, Koning CC, *et al*. (2009). Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: a systematic review. Radiotherapy & Oncology 93: 168-173.

Ramsay C, Pickard R, Robertson C, *et al*. (2012). Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health Technology Assessment 16(41): iv-313.

Rapiti E, Fioretta G, Verkooijen HM, *et al*. (2008). Increased risk of colon cancer after external radiation therapy for prostate cancer. International Journal of Cancer 123(5): 1141-1145.

Sahakitrungruang C, Patiwongpaisarn A, Kanjanaslip P *et al*. (2012). A randomized controlled trial comparing colonic irrigation and oral antibiotics administration versus 4% formalin application for treatment of hemorrhagic radiation proctitis. Diseases of the colon and rectum 55(10): 1053-1058.

Salminen E, Elomaa I, Minkkinen J, *et al*. (1988). Preservation of intestinal integrity during radiotherapy using live Lactobacillus acidophilus cultures. Clinical radiology 39: 435-437.

Sathya, J. R., Davis, I. R., Julian, J. A., Guo, Q., Daya, D., Dayes, I. S., Lukka, H. R. & Levine, M. (2005) Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 23: 1192-1199.

Selvadurai ED, Singhera M, Thomas K, *et al*. Medium-term outcomes of active surveillance for localised prostate cancer. Eur Urol 2013; http://dx.doi.org/10.1016/j.eururo.2013.02.020.

Sidik S, Hardjodisastro D, Setiabudy R, *et al*. (2007). Does hyperbaric oxygen administration decrease side effect and improve quality of life after pelvic radiation? Acta medica Indonesiana 39: 169-173.

Strauss HJ and Zeigler LH (1975). The Delphi technique and its uses in social science research. The Journal of Creative Behavior 9: 253-259.

Stolzenburg JU, Franz T, Kallidonis P, *et al*. (2011). Comparison of the FreeHand robotic camera holder with human assistants during endoscopic extraperitoneal radical prostatectomy. BJU International 107(6): 970-974.

Tewari A, Srivasatava A, Menon M, *et al*. (2003). A prospective comparison of radical retropubic and robot assisted prostatectomy: experience in one institution. BJU Int 92: 205–10.

Timko J. (2010). Probiotics as prevention of radiation-induced diarrhoea. Journal of Radiotherapy in Practice 9(4): 201-208.

Urbancsek H, Kazar T, Mezes I, *et al*. (2001). Results of a double-blind, randomized study to evaluate the efficacy and safety of Antibiophilus in patients with radiation-induced diarrhoea. European Journal of Gastroenterological Hepatology 13: 391-396.

Update 2014

Volk RJ, Cantor SB, Cass AR, Spann SJ, Weller SC, Krahn MD. Preferences of husbands and wives for outcomes of prostate cancer screening and treatment. J Gen Intern Med 2004;19:339-48.

Willis DL, Gonzalgo ML, Brotzman M, *et al*. (2012). Comparison of outcomes between pure laparoscopic vs robot-assisted laparoscopic radical prostatectomy: a study of comparative effectiveness based upon validated quality of life outcomes. BJU International 109(6): 898-905.

Wolanski P, Chabert C, Jones L, *et al* (2012). Preliminary results of robot-assisted laparoscopic radical prostatectomy (RALP) after fellowship training and experience in laparoscopic radical prostatectomy (LRP). BJU International 110(Suppl 4): 64-70.

Wong WW, Vora SA, Schild SE, *et al*. (2009). Radiation dose escalation for localized prostate cancer: intensity-modulated radiotherapy versus permanent transperineal brachytherapy. Cancer 115: 5596-5606.

Wachter S, Gerstner N, Goldner G, *et al*. (2000). Endoscopic scoring of late rectal mucosal damage after conformal radiotherapy for prostatic carcinoma. Radiotherapy & Oncology 54(1): 11-19.

Update 2014

5 Managing relapse after radical treatment

5.1 Introduction

Biochemical relapse after radical treatment for localised prostate cancer is now a common clinical problem in prostate cancer clinics. The challenge is identifying those men in whom biochemical relapse predicts a significant risk of prostate cancer morbidity or mortality.

Prostate specific antigen (PSA)[m] is a protein produced almost exclusively by prostatic epithelial cells, either benign or malignant. Radical treatment is aimed at the destruction of cancer cells and as a consequence also destroys benign prostatic tissue.

5.2 Defining biochemical relapse

The definition of biochemical relapse differs depending upon the radical treatment. Radical surgery aims to remove all prostatic tissue. The serum PSA should drop to very low levels (typically < 0.1ng/ml) and remain at that level. Radiation also results in cell death and a fall in serum PSA. A rise in PSA during follow-up indicates the probability of prostatic cancer cells present locally at the site of the prostate or at distant sites. However, this frequently does not translate into clinical recurrence or death from cancer.

The rate at which PSA increases following radical treatment is an important predictor of subsequent prostate cancer related mortality. Other factors such as Gleason score ≥ 8 and the timing of PSA rise after radical treatment are also useful measures of risk. The interpretation of biochemical relapse may be complicated by the variety of PSA assays available.

Recommendation	**Analyse serial PSA levels after radical treatment using the same assay technique. [2008]**
Qualifying statement	There was GDG consensus based on the known variability in assays to make this recommendation.

5.2.1 After radical prostatectomy

The presence of any detectable PSA in peripheral blood is often interpreted as indicating a clinically significant relapse, but this may be due to the presence of benign prostate tissue in a small proportion of men. The existence of residual disease, which may lead to clinical progression, can be recognised most reliably by serial PSA measurement.

5.2.2 After radical radiotherapy

The PSA does not usually fall to zero after radical treatment with external beam radiotherapy. The definitions of biochemical relapse with the best combination of sensitivity and specificity for clinical or distant relapse after radical treatment are those that used a fixed value above a nadir. This allows for the slight rise in PSA that is seen when neoadjuvant or adjuvant hormonal therapy is discontinued. The 2005 ASTRO consensus definition (PSA greater than current nadir + 2 ng/ml: Roach, 2006), had a sensitivity of 74% and specificity of 71% for any clinical failure.

m For more information on PSA please see Appendix 1.

5.2.13 After brachytherapy – low dose

Typically the PSA level falls slowly after brachytherapy and does not normally reach zero. Indeed, the level may temporarily rise (the PSA bounce) after initial treatment. The most sensitive and specific predictors of persistent disease or relapse are, as with external beam radiotherapy; the nadir + 2 ng/ml.

Clinical evidence (2008)

Evidence from case series and clinical trials shows that not all men with biochemical relapse after definitive prostate cancer therapy experience distant metastasis or death from prostate cancer (Vicini *et al*. 2005; Pound *et al*. 1999). Given this, studies have examined factors that signify clinically relevant biochemical recurrence. A PSA doubling time of less than 3 months was an adverse prognostic factor for cancer specific survival (Freedland *et al*. 2005; D'Amico *et al*. 2004) and overall survival (D'Amico *et al*. 2004) in a series of men with biochemical relapse. Gleason score was a prognostic factor for disease specific survival (Freedland *et al*. 2005; Kwan *et al*. 2006).

Definitions of biochemical relapse

After prostatectomy

Reviews report a variety of biochemical relapse definitions in the literature (Vincini 2005; Cookson *et al*. 2007), most commonly PSA of 0.4 ng/ml or more and rising and PSA of 0.2 ng/ml or more and rising (Cookson *et al*. 2007). Stephenson *et al*. (2006) compared definitions of biochemical relapse in a large series of men following prostatectomy. The definition that best correlated with metastatic progression was PSA of 0.4 ng/ml or more and rising. A recent ASTRO consensus panel favoured a definition of 0.2 ng/ml or more and rising due to its greater sensitivity (Cookson *et al*. 2007).

After external beam radiotherapy (EBRT)

Meta-analysis of individual patient data was used to test 102 definitions of biochemical recurrence after external beam radiotherapy (Kuban *et al*. 2005; Horwitz *et al*. 2005). The definitions with the best sensitivity and specificity for clinical and distant failure were those using a fixed PSA rise (2 or 3 ng/ml) above the current nadir value at call.

After brachytherapy

Kuban *et al*. (2006) reported the most sensitive and specific practical definitions of biochemical recurrence after brachytherapy were the current nadir + 1ng/ml and the current nadir + 2 ng/ml (ASTRO 2005). The sensitivity and specificity of the ASTRO 2005 definition were comparable to those seen in the radiotherapy cohort (Kuban *et al*. 2005; Horwitz *et al*. 2005). The ASTRO 2005 definition had a false call rate of 2% due to PSA bounce in a large series of men after external beam radiotherapy or brachytherapy for prostate cancer (Pickles 2006).

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

5.3 Assessment of biochemical relapse

If biochemical relapse is confirmed, options for investigation may include biopsy, local (pelvic) imaging and imaging for the presence of metastatic disease.

5.3.1 Biopsy

Biopsy of the prostatic bed after radical prostatectomy can identify the existence of local recurrence. However, a positive biopsy does not exclude metastatic disease and a negative biopsy does not exclude local recurrence. Therefore the results of the biopsy are not useful for making treatment decisions. After radiotherapy, including brachytherapy, routine biopsy of the prostate does not add clinically useful information to that obtained from serial PSA measurement.

Recommendation	**Do not offer biopsy of the prostatic bed to men with prostate cancer who have had a radical prostatectomy. [2008]** **Offer biopsy of the prostate after radiotherapy only to men with prostate cancer who are being considered for local salvage therapy in the context of a clinical trial. [2008]**
Qualifying statement	These recommendations are based on evidence from small case series.

Clinical evidence (2008)

Reported rates of positive biopsy in case series of men with biochemical recurrence after prostatectomy ranged from 41 to 55% (Scattoni *et al*. 2004). Men with eventual positive biopsy often required more than one biopsy session, suggesting a significant risk of false negative. An ASTRO consensus panel (Cox *et al*. 1999) considered evidence from case series about prostate biopsy after radiotherapy and concluded that routine biopsy of the prostate after radiotherapy was not recommended since it did not add to data provided by serial PSA measurements.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

5.3.2 Imaging

Magnetic resonance imaging (MRI) scanning may have some value in those with biochemical relapse being considered for further local therapy. It may detect significant extracapsular disease, seminal vesicle involvement or lymphadenopathy which might preclude radical salvage therapy.

The chance of finding skeletal metastases in men with biochemical relapse is best predicted by the absolute PSA level and the rate of rise.

Recommendation	**For men with evidence of biochemical relapse following radical treatment and who are considering radical salvage therapy:** • **do not offer routine MRI scanning prior to salvage radiotherapy in men with prostate cancer** • **offer an isotope bone scan if symptoms or PSA trends are suggestive of metastases. [2008]**
Qualifying statement	These recommendations are based on case series evidence and GDG consensus.

Clinical evidence (2008)

The literature search found no studies reporting the impact of staging after biochemical recurrence on patient outcomes. Small case series report good sensitivity and specificity of

MRI for the detection of local recurrence after prostatectomy (Sella *et al*. 2004; Silverman & Krebs 1997), but not after radiotherapy (Sala *et al*. 2006; Coakley 2004).

The rate of bone scans positive for malignancy in men with biochemical recurrence after radical prostatectomy was 4 to 14% in four case series (Cher *et al*. 1998; Dotan 2005; Okotie *et al*. 2004; Kane 2003). The rate of suspicious or indeterminate (but ultimately non-malignant) scans was almost as high at between 3 and 8%, raising questions about the specificity of the bone scan. Trigger PSA, PSA slope, and PSA velocity were all significant predictors of bone scan result. The risk of a positive bone scan for men with PSA less than 10ng/ml was between 1 and 3% in two series (Cher *et al*. 1998; Okotie *et al*. 2004), compared with 75% for PSA greater than 10 ng/ml (Okotie *et al*. 2004).

In one series salvage treatment decisions were sometimes changed on the basis of ProstaScint imaging (Jani 2004), however there was inconsistent evidence that ProstaScint results could predict the outcome of salvage therapy (Levesque *et al*. 1998; Proano 2006; Mohideen 2002; Thomas *et al*. 2003 Nagda *et al*. 2007).

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

5.4 Management of biochemical relapse

It is not known whether treating biochemical relapse, rather than waiting until there are clinical signs of disease, will influence survival.

Biochemical relapse after radical treatment, in many cases, does not lead to metastases or death from prostate cancer. Whether men with biochemical relapse should be treated depends in part on the timing and rate of rise of PSA as a predictor of clinical progression. Management options can be divided into local salvage therapies and systemic therapies.

Recommendation	**Biochemical relapse (a rising PSA) alone should not necessarily prompt an immediate change in treatment. [2008]** **Biochemical relapse should trigger an estimate of PSA doubling time, based on a minimum of 3 measurements over at least a 6 month period. [2008]**
Qualifying statement	There is evidence from longitudinal studies and clinical trials to support making these recommendations.

5.4.1 Local salvage therapy

5.4.1.1 For men with biochemical relapse following radical prostatectomy

There is large variation in the UK in the selection of men for salvage radiotherapy: whether to give radiotherapy as soon as relapse is confirmed or when a PSA threshold is reached; whether to treat just the prostate bed or surrounding tissues as well; and whether or not to use adjuvant hormonal therapy in addition.

Recommendation	**Offer men with biochemical relapse after radical prostatectomy, with no known metastases, radical radiotherapy to the prostatic bed. [2008]**
Qualifying statement	There is a range of evidence to support this recommendation.

Recommendation	**Men with biochemical relapse should be considered for entry to appropriate clinical trials. [2008]**
Qualifying statement	This recommendation is based on GDG consensus.

5.4.11 For men with biochemical relapse following radical radiotherapy (external beam or brachytherapy)

Salvage local therapies for biochemical relapse after radiotherapy (external beam or brachytherapy) include radical prostatectomy, cryotherapy and high intensity focused ultrasound. Radical prostatectomy as salvage has been shown to produce biochemical control in highly selected men but carries a higher risk of incontinence, impotence and rectal damage than when used as primary treatment.

Research recommendation	**Clinical trials should be set up to examine the effect of local salvage therapies on survival and quality of life in men with biochemical relapse after radiotherapy. [2008]**
Why is this important	Salvage local therapies after radiotherapy include radical prostatectomy, cryotherapy and HIFU, but little evidence exists to support their use, and there may be a higher risk of incontinence, impotence and rectal damage than when used as primary treatment.

5.4.12 Systemic therapy

Hormonal therapy may control symptomatic, progressive or metastatic disease following either surgery or radiation. There are variations in practice with regard to the indications for, and the timings of, hormonal therapy in these situations. Other systemic therapies are being investigated in continuing clinical trials.

Recommendation	**Do not routinely offer hormonal therapy to men with prostate cancer who have a biochemical relapse unless they have:** • **symptomatic local disease progression, or** • **any proven metastases, or** • **a PSA doubling time of < 3 months. [2008]**
Qualifying statement	There is evidence from randomised controlled trials to support this recommendation.

Clinical evidence (2008)

There was little evidence about salvage prostatectomy. Estimates of disease specific survival (Bianco *et al*. 2005; Ward *et al*. 2005) (Sanderson, 2006) and complication rates (Stephenson *et al*. 2004; Ward *et al*. 2005) (Sanderson, 2006) are derived from case series. The NICE interventional procedures guidance on salvage cryotherapy (National Institute for Health and Clinical Excellence 2005) reviewed seven case series with limited follow-up. Five year disease specific survival was 79%, in the only study reporting this outcome.

A systematic review (Nilsson, Norlen, & Widmark 2004) of ten retrospective case series, concluded that after radical prostatectomy (with adverse factors) adjuvant EBRT seems to result in better disease free survival than salvage or no postoperative EBRT. Similarly salvage EBRT probably results in marginally better outcome than no salvage EBRT. One study (Macdonald *et al*. 2004) reported outcomes after salvage radiotherapy in a series of men with biochemical recurrence only and in men with palpable recurrence. Five year overall survival was 95% in men treated for biochemical recurrence compared to 76% for men with palpable recurrence.

The literature search did not identify any randomised trials of the treatment of PSA-only recurrence. Indirect evidence comes from a systematic review (Wilt *et al*. 2001) of four

randomised control trials (RCTs) of immediate versus deferred hormonal therapy in men with advanced prostate cancer. Meta-analysis showed a small, but not statistically significant improvement in overall and disease specific survival at 1, 2 and 5 years, in favour of early therapy. The review concluded that there was insufficient evidence about the use of androgen suppression in men with clinically localised disease, who experience biochemical recurrence without other signs or symptoms. Moul *et al*. (2004) considered the timing of hormonal therapy in a large case series of men with biochemical recurrence. There was no difference between the metastasis free survival of early and delayed hormonal therapy groups. A subgroup analysis, however, showed significantly better metastasis free survival for high-risk patients treated with early hormonal therapy.

Cost-effectiveness evidence (2008)

The literature review on the management of biochemical relapse identified 20 potentially relevant papers but none were obtained for appraisal as they did not include any economic evaluations. Since case studies represented the highest quality clinical evidence, the evidence base was considered too weak to warrant any further consideration of cost-effectiveness and de novo economic modelling.

5.5 References

2008

Bianco, F. J., Scardino, P. T., Stephenson, A. J., Diblasio, C. J., Fearn, P. A. & Eastham, J. A. (2005) Long-term oncologic results of salvage radical prostatectomy for locally recurrent prostate cancer after radiotherapy. Int J Radiat.Oncol Biol.Phys., 62: 448–453.

Cher, M. L., Bianco, F. J., Lam, J. S., Davis, L. P., Grignon, D. J., Sakr, W. A., Banerjee, M., Pontes, J. E. & Wood, D. P. (1998) Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. J Urol, 160: 1387–1391.

Coakley, F. (2004) Endorectal MR imaging MR spectroscopic imaging for locally recurrent prostate cancer after external beam radiation therapy: Preliminary experience. Radiology, 233: 441–448.

Cookson, M. S., Aus, G., Burnett, A. L., Canby-Hagino, E. D., D'Amico, A. V., Dmochowski, R. R., Eton, D. T., Forman, J. D., Golden- berg, S. L., Hernandez, J., Higano, C. S., Kraus, S. R., Moul, J. W., Tangen, C., Thrasher, J. B. & Thompson, I. (2007) Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the re. J Urol, 177: 540–545.

Cox, J. D., Gallagher, M. J., Hammond, E. H., Kaplan, R. S., Schellhammer, P. F., Crook, J. M., Leibel, S. A., Forman, J. D., Grimm, P. D., Zietman, A. L., Hudson, M. A., Schild, S. A., Beyer, D. C., Hussey, D. H., Thames, H. & Shipley, W. U. (1999)

Consensus statements on radiation therapy of prostate cancer: Guidelines for prostate re-biopsy after radiation and for radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. J Clin Oncol, 17: 1155–1163.

D'Amico, A. V., Moul, J., Carroll, P. R., Sun, L., Lubeck, D. & Chen, M. H. (2004) Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy. J Urol, 172: S42-S46.

Dotan (2005). Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectorny. J Clin Oncol 23.

Freedland, S. J., Humphreys, E. B., Mangold, L. A., Eisenberger, M., Dorey, F. J., Walsh, P. C. & Partin, A. W. (2005) Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy.[see comment]. JAMA, 294: 433–439.

Horwitz, E. M., Thames, H. D., Kuban, D. A., Levy, L. B., Kupelian, P. A., Martinez, A. A., Michalski, J. M., Pisansky, T. M., Sandler, H. M., Shipley, W. U., Zelefsky, M. J., Hanks, G. E. & Zietman, A. L. (2005) Definitions of biochemical failure that best predict clinical failure in patients with prostate cancer treated with external beam radiation alone: a multi-institutional pooled analysis. J Urol, 173: 797–802.

Jani, A. (2004) Influence of radioimmunoscintigraphy on postprostatectomy radiotherapy treatment decision making. J Nucl Med, 45: 571. Kane. (2003) Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. Urology, 61.

Kuban, D. A., Thames, H. D. & Shipley, W. U. (2005) Defining recurrence after radiation for prostate cancer. [Review] [34 refs]. J Urol, 173: 1871–1878.

Kuban, D. A., Levy, L. B., Potters, L., Beyer, D. C., Blasko, J. C., Moran, B. J., Ciezki, J. P., Zietman, A. L., Zelefsky, M. J., Pisansky, T. M., Elshaikh, M. & Horwitz, E. M. (2006) Comparison of biochemical failure definitions for permanent prostate brachytherapy. Int J Radiat.Oncol Biol.Phys., 65: 1487–1493.

Kwan, W., Pickles, T., Duncan, G., Liu, M. & Paltiel, C. (2006) Relationship between delay in radiotherapy and biochemical control in prostate cancer. Int J Radiat.Oncol Biol.Phys., 66: 663–668.

Levesque, P. E., Nieh, P. T., Zinman, L. N., Seldin, D. W. & Libertino, J. A. (1998) Radiolabeled monoclonal antibody indium 111-labeled CYT-356 localizes extraprostatic recurrent carcinoma after prostatectomy. Urology, 51: 978–984.

Macdonald, O. K., Schild, S. E., Vora, S., Andrews, P. E., Ferrigni, R. G., Novicki, D. E., Swanson, S. K. & Wong, W. W. (2004) Salvage radiotherapy for men with isolated rising PSA or locally palpable recurrence after radical prostatectomy: do outcomes differ? Urology, 64: 760–764.

Mohideen, N. (2002) Role of Prostascint scan in the assessment of patients who undergo radiotherapy for biochemical failure after radical prostatectomy for prostate cancer. J Urol, 167: 174.

Moul, J. W., Wu, H., Sun, L., McLeod, D. G., Amling, C., Donahue, T., Kusuda, L., Sexton, W., O'Reilly, K., Hernandez, J., Chung, A. & Soderdahl, D. (2004) Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. J Urol, 171: 1141–1147.

Nagda, S. N., Morideen, N., Lo, S. S., Khan, U., Dillehay, G., Wagner, R., Campbell, S. & Flanigan, R. (2007) Long-term follow-up of In-111-capromab pendetide (ProstaScint) scan as pretreatment assessment in patients who undergo salvage radiotherapy for rising prostate-specific antigen after radical prostatectomy for prostate cancer. International Journal of Radiation Oncology Biology Physics, 67: 834–840.

National Institute for Health and Clinical Excellence (2005) Cryotherapy for recurrent prostate cancer. Interventional Procedure Guidance 119.

Nilsson, S., Norlen, B. J. & Widmark, A. (2004) A systematic overview of radiation therapy effects in prostate cancer. [Review] [390 refs]. Acta Oncol, 43: 316–381.

Okotie, O. T., Aronson, W. J., Wieder, J. A., Liao, Y., Dorey, F., deKernion, J. B. & Freedland, S. J. (2004) Predictors of metastatic disease in men with biochemical failure following radical prostatectomy. J Urol, 171: 2260–2264.

Pickles, T. (2006) Prostate-specific antigen (PSA) bounce and other fluctuations: Which biochemical relapse definition is least prone to PSA false calls? An analysis of 2030 men treated for prostate cancer with external beam or brachytherapy with or without adjuvant androge. International Journal of Radiation Oncology Biology Physics, 64: 1355–1359.

Pound, C. R., Partin, A. W., Eisenberger, M. A., Chan, D. W., Pearson, J. D. & Walsh, P. C. (1999) Natural history of progression after PSA elevation following radical prostatectomy. JAMA, 281: 1591–1597.

Proano, J. (2006) The impact of a negative (111)indium-capromab pendetide scan before salvage radiotherapy. J Urol, 175: 1668–1672. Roach, M., Hanks, G., Thames, H., Schellhammer, P., Shipley, W. U., Sokol, G. H. & Sandler, H. (2006) Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat.Oncol Biol.Phys., 65: 965–974.

Sala, E., Eberhardt, S. C., Akin, O., Moskowitz, C. S., Onyebuchi, C. N., Kuroiwa, K., Ishill, N., Zelefsky, M. J., Eastham, J. A. & Hricak, H. (2006) Endorectal MR imaging before salvage prostatectomy: tumor localization and. Radiology., 238: 176–183.

Sanderson, K. M., Penson, D. F., Cai, J., Groshen, S., Stein, J. P., Lieskovsky, G. & Skinner, D. G. (2006) Salvage radical prostatectomy: quality of life outcomes and long-term oncological control of radiorecurrent prostate cancer. J Urol, 176: 2025–2031.

Scattoni, V., Montorsi, F., Picchio, M., Roscigno, M., Salonia, A., Rigatti, P. & Fazio, F. (2004) Diagnosis of local recurrence after radical prostatectomy. [Review] [58 refs]. BJU Int, 93: 680–688.

Sella, T., Schwartz, L. H., Swindle, P. W., Onyebuchi, C. N., Scardino, P. T., Scher, H. I. & Hricak, H. (2004) Suspected local recurrence after radical prostatectomy: endorectal coil MR imaging. Radiology, 231: 379–385.

Silverman, J. M. & Krebs, T. L. (1997) MR imaging evaluation with a transrectal surface coil of local recurrence of prostatic cancer in men who have undergone radical prostatectomy. AJR Am J Roentgenol., 168: 379–385.

Stephenson, A. J., Kattan, M. W., Eastham, J. A., Dotan, Z. A., Bianco, F. J., Lilja, H. & Scardino, P. T. (2006) Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. J Clin Oncol, 24: 3973–3978.

Stephenson, A. J., Scardino, P. T., Bianco Jr, F. J., Diblasio, C. J., Fearn, P. A. & Eastham, J. A. (2004) Morbidity and functional outcomes of salvage radical prostatectomy for locally recurrent prostate cancer after radiation therapy. J Urol, 172: 2239–2243.

Thomas, C. T., Bradshaw, P. T., Pollock, B. H., Montie, J. E., Taylor, J. M., Thames, H. D., McLaughlin, P. W., DeBiose, D. A., Hussey, D. H. & Wahl, R. L. (2003) Indium-111-capromab pendetide radioimmunoscintigraphy and prognosis for durable biochemical response to salvage radiation therapy in men after failed prostatectomy.[see comment]. J Clin Oncol, 21: 1715–1721.

Vicini, F. A., Vargas, C., Abner, A., Kestin, L., Horwitz, E. & Martinez, A. (2005) Limitations in the use of serum prostate specific antigen levels to monitor patients after treatment for prostate cancer. J Urol, 173: 1456–1462.

Ward, J. F., Sebo, T. J., Blute, M. L. & Zincke, H. (2005) Salvage surgery for radiorecurrent prostate cancer: Contemporary outcomes. J Urol, 173: 1156–1160.

Wilt, T., Nair, B., MacDonald, R. & Rutks, I. Early versus deferred androgen suppression in the treatment of advanced prostatic cancer [Cochrane review]. 2001 ;(4):

6 Locally advanced prostate cancer

6.1 Introduction

There is no universally agreed definition of locally advanced prostate cancer. For the purposes of this guideline, this includes:

- High-risk localised prostate cancer (as defined in chapter 4)
- T3b and T4, N0 prostate cancer
- any T, N1 prostate cancer

The majority of such men can be treated with radical intent if they have no significant comorbidites. Most men with locally advanced prostate cancer will receive hormone therapy as at least part of their treatment. Typically this would be androgen deprivation therapy although bicalutamide monotherapy is sometimes used as an alternative.

Update 2014

6.2 Combined hormone and radiotherapy

6.2.1 Neoadjuvant and adjuvant hormone therapy

Hormonal therapy is sometimes given for several months before radical treatment (neoadjuvant therapy).

Hormonal therapy has been used following both surgery and radiotherapy (adjuvant therapy) with the intention of improving survival. The use of adjuvant hormonal therapy after radical prostatectomy has not been updated as part of this guideline.

Combining hormone therapy and radiotherapy treatments may therefore provide optimal local and distant tumour control, but is only relevant to those patients where radiotherapy alone would not encompass and eliminate the full extent of the prostate cancer. The hormones may be given for a variable length of time and may precede, be given during and for a period following radiotherapy. The optimal timing and overall duration is uncertain.

Update 2014

The side effects of hormonal therapy can be substantial, especially if given for several years, and so the risk/benefit ratio needs to be considered.

Recommendation	**Do not offer adjuvant hormonal therapy in addition to radical prostatectomy, even to men with margin-positive disease, other than in the context of a clinical trial. [2008]**
Qualifying statement	There is evidence from randomised controlled trials of a lack of clinical benefit and significant toxicity to support making this recommendation.

Clinical evidence (2008)

Evidence about neoadjuvant and adjuvant hormonal therapy comes from a systematic review (Kumar *et al*. 2006) of 21 randomised controlled trials.

Adjuvant therapy with radical prostatectomy

Randomised trials report significant toxicity with adjuvant therapy in addition to prostatectomy (Kumar *et al*. 2006). With the exception of one small trial in node-positive men (Messing *et al*. 1999), these trials have not demonstrated significant benefit in overall survival. It is possible that modest survival benefits will emerge with longer follow-up.

Clinical question: Which patients with non-metastatic prostate cancer benefit from a combination of hormones and external beam radiotherapy?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all pre-specified outcomes is summarised in Tables 47 and 48.

Overall survival

Nine studies involving 5,994 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with longer overall survival (HR 1.3 95% CI 1.2-1.41).

Four studies involving 2,725 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy followed by hormone therapy is associated with longer overall survival (HR 1.32 95% CI 1.17-1.47).

Three studies involving 2,972 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with hormone therapy followed by radiotherapy is associated with longer overall survival (HR 1.25 95% CI 1.12-1.39).

Two studies involving 297 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with neoadjuvant, concomitant and adjuvant hormone therapy plus radiotherapy is associated with longer overall survival (HR 1.72 95% CI 1.25-2.39).

Four studies involving 2,533 patients provided moderate quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with similar or longer overall survival (not pooled).

Disease-free survival

Seven studies involving 3,892 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with longer disease-free survival (HR = 1.49 95% CI 1.37-1.62).

Four studies involving 2,808 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy followed by hormone therapy is associated with longer disease-free survival (HR 1.48 95% CI 1.33-1.64).

Two studies involving 993 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with hormone therapy followed by radiotherapy is associated with longer disease-free survival (HR 1.47 95% CI 1.28-1.68).

One study involving 91 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with neoadjuvant, concomitant and adjuvant hormone therapy plus radiotherapy is associated with longer disease-free survival (HR 2.51 95% CI 1.32-4.76).

Two studies involving 1,469 patients provided low quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with longer disease-free survival (not pooled).

Update 2014

Distant metastases-free survival

Five studies involving 4,332 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with longer metastases-free survival (HR 1.63 95% CI 1.43-1.85).

Two studies involving 1,360 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy followed by hormone therapy is associated with longer distant metastasis-free survival (HR 1.73 95% CI 1.46-2.06).

Three studies involving 2,972 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with hormone therapy followed by radiotherapy is associated with longer distant metastasis-free survival (HR 1.49 95% CI 1.22-1.82).

Two studies involving 452 patients provided low quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with similar distant metastasis-free survival (not pooled).

Biochemical disease-free survival

One study involving 5,903 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy followed by hormone therapy is associated with longer biochemical-free survival (HR 1.62 95% CI 1.39-1.88).

Four studies involving 3,109 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with hormone therapy followed by radiotherapy is associated with longer biochemical-free survival (HR 1.65 95% CI 1.48-1.83).

Two studies involving 338 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with neoadjuvant, concomitant and adjuvant hormone therapy plus radiotherapy is associated with longer biochemical-free survival (HR 2.53 95% CI 1.75-3.67).

Two studies involving 1,139 patients provided low quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with longer biochemical-free survival (not pooled).

Adverse events

Five studies involving 4,813 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with comparable rates of adverse events (not pooled).

Two studies involving 2,080 patients provided low quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with comparable rates of adverse events (not pooled).

Cardiovascular events

Five studies involving 3,988 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with comparable rates of cardiovascular events (not pooled).

One study involving 263 patients provided moderate quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with comparable rates of cardiovascular events (not pooled).

Update 2014

Health-related quality of life

One study involving 1,979 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with lower health-related quality of life.

Two studies involving 2,080 patients provided low quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with comparable health-related quality of life (not pooled).

Update 2014

Table 47: GRADE profile: which patients with non-metastatic prostate cancer benefit from a combination of hormones and external beam radiotherapy? Comparison: radiotherapy alone (RT) versus radiotherapy plus hormone therapy (RT+HT)

Quality assessment							Number of events		Effect			Quality
No. of studies *	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT	RT + HT	HR	95% CI	Absolute	
Overall survival (follow-up 7.2-19.0 years)												
9[1]	RCTs	Serious[2]	None	Serious[3]	None	None	1373 / 2989 (45.9%)	1160 / 3005 (38.6%)	1.3	1.2 – 1.4	84 more per 1000 (from 57 more to 111 more)	LOW ⊕⊕OO
Overall survival – RT alone vs RT followed by HT (follow-up 7.2-18.0 years)												
4[4]	RCTs	Serious[2]	None	Serious[3]	None	None	634 / 1345 (47.1%)	550 / 1380 (39.9%)	1.32	1.17 – 1.47	90 more per 1000 (from 50 more to 128 more)	LOW ⊕⊕OO
Overall survival – RT alone vs HT followed by RT (follow-up 9.1-13.2 years)												
3[5]	RCTs	Serious[2]	None	Serious[3]	None	None	695 / 1494 (46.5%)	580 / 1478 (39.2%)	1.25	1.12 – 1.39	71 more per 1000 (from 35 more to 107 more)	LOW ⊕⊕OO
Overall survival – RT alone vs neoadjuvant, concomitant & adjuvant HT + RT (follow-up 7.6-19.0 years)												
2[6]	RCTs	Serious[7]	None	Serious[3]	Very serious[8]	None	44 / 150 (29.3%)	30 / 147 (20.4%)	1.72	1.25 – 2.39	121 more per 1000 (from 44 more to 216 more)	VERY LOW ⊕OOO
Disease-free survival (follow-up 7.2-18.0 years)												
7[9]	RCTs	Serious[2]	None	Serious[3]	None	Reporting bias[10]	1279 / 1935 (66.1%)	1047 / 1957 (53.5%)	1.49	1.37 – 1.62	145 more per 1000 (from 115 more to 176 more)	VERY LOW ⊕OOO
Disease-free survival – RT alone vs RT followed by HT (follow-up 7.2-18.0 years)												
4[11]	RCTs	Serious[2]	None	Serious[3]	None	None	791 / 1387	663 / 1421	1.48	1.33 – 1.64	139 more per 1000 (from 100 more to 177 more)	LOW ⊕⊕OO

Quality assessment							Number of events		Effect			Quality
No. of studies *	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT	RT + HT	HR	95% CI	Absolute	
							(57.0%)	(46.7%)				
Disease-free survival – RT alone vs HT followed by RT (follow-up 10.6-13.2 years)												
2[12]	RCTs	Serious[2]	None	Serious[3]	None	None	460 / 502 (91.6%)	370 / 491 (75.4%)	1.47	1.28 – 1.68	119 more per 1000 (from 80 more to 151 more)	VERY LOW ⊕OOO
Disease-free survival – RT alone vs neoadjuvant, concomitant & adjuvant HT + RT												
1[14]	RCTs	Serious[7]	None	Serious[3]	Very serious[8]	Reporting bias[15]	28 / 46 (60.9%)	14 / 45 (31.1%)	2.51	1.32 – 4.76	296 more per 1000 (from 77 more to 519 more)	VERY LOW ⊕OOO
Distant metastases-free survival (follow-up 9.1-18.0 years)												
5[16]	RCTs	Serious[2]	None	Serious[3]	None	Reporting bias[17]	407 / 2170 (18.8%)	291 / 2162 (13.5%)	1.63	1.43 – 1.85	75 more per 1000 (from 52 more to 100 more)	VERY LOW ⊕OOO
Distant metastases-free survival – RT alone vs RT followed by HT (follow-up 9.1-18.0 years)												
2[19]	RCTs	Serious[2]	None	Serious[3]	None	Reporting bias[20]	183 / 676 (27.1%)	128 / 684 (18.7%)	1.73	1.46 – 2.06	114 more per 1000 (from 74 more to 160 more)	VERY LOW ⊕OOO
Distant metastases-free survival – RT alone vs HT followed by RT (follow-up 9.1-13.2 years)												
3[21]	RCTs	Serious[2]	None	Serious[3]	None	None[22]	224 / 1494 (15.0%)	224 / 1478 (11.0%)	1.49	1.22 – 1.82	50 more per 1000 (from 23 more to 81 more)	LOW ⊕⊕OO
Distant metastases-free survival – RT alone vs neoadjuvant, concomitant & adjuvant HT + RT												
0	-	-	-	-	-	-	-	-	-	-	-	-
Biochemical disease-free survival (follow-up 5.0-13.2 years)												
6[23]	RCTs	Serious[2]	None	Serious[3]	None	Reporting bias[24]	No overall estimate is provided because the same data from the RT alone group in the study by Laverdiere are used in two subgroups.					VERY LOW ⊕OOO
Biochemical disease-free survival – RT alone vs RT followed by HT (follow-up 7.1-7.2 years)												

Quality assessment							Number of events		Effect			Quality
No. of studies *	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT	RT + HT	HR	95% CI	Absolute	
1[25]	RCTs	Serious[26]	None	Serious[3]	None	Reporting bias[27]	358 / 671 (53.4%)	303 / 699 (43.3%)	1.62	1.39 – 1.88	168 more per 1000 (from 113 more to 223 more)	VERY LOW ⊕OOO
Biochemical disease-free survival – RT alone vs HT followed by RT (follow-up 5.0-13.2 years)												
4[28]	RCTs	Serious[2]	None	Serious[3]	None	None	836 / 1562 (53.5%)	569 / 1547 (36.8%)	1.65	1.48 – 1.83	163 more per 1000 (from 125 more to 200 more)	LOW ⊕⊕OO
Biochemical disease-free survival – RT alone vs neoadjuvant, concomitant & adjuvant HT + RT (follow-up 5.0-7.6 years)												
2[29]	RCTs	Serious[2]	None	Serious[3]	Serious[8]	None	85 / 171 (49.7%)	42 / 167 (25.1%)	2.53	1.75 – 3.67	268 more per 1000 (from 146 more to 403 more)	VERY LOW ⊕OOO
Adverse events (follow-up 7.6-13.2 years)												
5[30]	RCTs	Serious[2]	None	Serious[3]	None	Reporting bias[17]	2269	2544	No apparent differences between the groups (not pooled)			VERY LOW ⊕OOO
Cardiovascular events (follow-up 7.2-18.0 years)												
5[31]	RCTs	Serious[2]	None	Serious[3]	None	Reporting bias[17]	1849	2139	No differences between the groups (not pooled)			VERY LOW ⊕OOO
Health-related quality of life (follow-up 0.0-14.1 years)												
1[32]	RCT	Serious[33]	None	Very serious[34]	None	Reporting bias[35]	992	987	Favours RT alone			VERY LOW ⊕OOO

1 Bolla 2010, D'Amico 2004, Denham 2011, Granfors 2006, Jones 2011, Roach 2008, RTOG 85-31, See 2006, Zagars 1988. 2 The studies are subject to a number of design limitations that render them at high or unknown risk of bias (see also the quality assessment undertaken for each study). 3 Apart from Jones 2011 and to some extent RTOG 85-31, it has not been possible to analyse the patients according to risk group (low, intermediate, high and locally advanced). 4 Bolla 2010, RTOG 85-31, See 2006, Zagars 1988. 5 Denham 2011, Jones 2011, Roach 2008. 6 D'Amico 2004, Granfors 2006. 7 It is unclear whether outcome assessment was conducted under blinded conditions in D'Amico 2004 and Granfors 2006 and the method of random sequence generation and allocation concealment are not reported by Granfors 2006. 8 The numbers of patients and events were low. 9 Bolla 2010, Denham 2011, Granfors 2006, Roach 2008, RTOG 85-31, See 2006, Zagars 1988. 10 3/10 included studies do not report this outcome. 11 Bolla 2010, RTOG 85-31, See 2006, Zagars 1988. 12 Denham 2011, Roach 2008. 13 2/4 included studies do not report this outcome. 14 Granfors 2006. 15 2/3 included studies do not report this outcome. 16 Bolla 2010, Denham 2011, Jones 2011, Roach 2008, RTOG 85-31. 17 5/10 included studies do not report this outcome. 18 Bolla 2010 did not report the event rate, thus the overall event rate reported here is lower than it actually is. 19 Bolla 2010, RTOG 85-31. 20

2/4 included studies do not report this outcome. 21 Denham 2011, Jones 2011, Roach 2008. 22 1/4 included studies does not report this outcome. 23 D'Amico 2004, Denham 2011, Jones 2011, Laverdiere 2004, Roach 2008, See 2006. 24 4/10 included studies do not report this outcome. 25 See 2006. 26 The study reports no information regarding random sequence generation, allocation concealment, and blinding of outcome assessment. 27 3/4 included studies do not report this outcome. 28 Denham 2011, Jones, 2011, Laverdiere 204, Roach 2008. 29 D'Amico 2004, Laverdiere 2004. 30 D'Amico 2004, Denham 2011, Jones 2011, Roach 2008, See 2006. 31 Bolla 2010, Denham 2011, Roach 2008, RTOG 85-31, See 2006. 32 Jones 2011. 33 It is unclear if the study employed adequate allocation concealment and blinded outcome assessment. 34 These data were not analysed according to risk group and only QoL data pertaining to erectile function reported. 35 9/10 included studies do not report this outcome.

Table 48: GRADE profile: which patients with non-metastatic prostate cancer benefit from a combination of hormones and external beam radiotherapy? Comparison: hormone therapy alone (HT) versus radiotherapy plus hormone therapy (RT+HT)

Quality assessment							Number of events		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HT	RT + HT	HR	95% CI	Absolute	
Overall survival (follow-up 5.6-8.0 years)												
4[1]	RCTs	Serious[2]	None	None[3]	None	None	1722	1476	5 years: No differences between the groups 8 years: Better survival in RT/HT group 10 years: Favours RT+HT			MODERATE
Disease-free survival (follow-up 5.6-6.0 years)												
2[4]	RCTs	Serious[2]	None	None[3]	None	Reporting bias[5]	773	736	Favours RT+HT			LOW
Distant metastases-free survival (follow-up 4.0-5.6 years)												
2[6]	RCTs	Serious[2]	None	None[3]	None	None	104	103	No differences between the groups			LOW
Biochemical disease-free survival (follow-up 5.6-7.6 years)												
2[7]	RCTs	Serious[2]	None	None[3]	None	None	570	569	Favours RT+HT			LOW
Adverse events (follow-up 5.6-7.6 years)												
3[8]	RCTs	Serious[2]	None	None[3]	None	Reporting bias[5]	1071	1289	No differences between the groups			LOW
Cardiovascular events (follow-up 5.6 years)												
1[9]	RCT	Serious[2]	None	None[3]	None	None	10	17	Similar rate between the groups			MODERATE
Health-related quality of life (follow-up median 7.6 years)												
2[8]	RCTs	Serious[2]	None	None[3]	None	Reporting bias[5]	1041	1039	Minor differences between the groups			LOW

1 Fellows et al. 1992, Mottet 2010, Warde [PR07], Widmark et al. 2009.

2 It was unclear whether Mottet 2010 and Fellows 1992 employed an adequate random sequence generation method and whether the outcome assessment was blinded in Mottet 2010. Fellows 1992, Warde [PR07] and Widmark et al. 2009 did not employ blinded outcome assessment.

Update 2014

3 Although the data were not analysed according to patient risk groups, the Guideline Development Group judged that the vast majority of the included patients were of at least intermediate risk.
4 Warde [PR07]. *5 ≤ 50% of the four included studies report this outcome.* *6 Fellows 1992; Mottet 2010* *7 Mottet 2010, Widmark et al. 2009.*
8 Warde [PR07], Widmark et al. 2009, Mottet 2012. Fellows 1992 did not report adverse events by treatment group in enough detail to include. *9Mottet 2010.*

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. No further economic analysis was undertaken partly because finding a group of patients that could benefit from hormones in combination with EBRT is primarily a clinical problem rather than an economic one. In addition, even if the topic was considered a high priority for economic analysis, the development of a model would have most likely been hindered by limitations in the clinical evidence base. In particular, the papers did not stratify patients into useful and consistent subgroups.

Recommendations	**Offer men with intermediate- and high-risk localised prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone. [new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of overall survival and metastases-free survival to be the most important as they reflect the likelihood of a patient staying alive. The other outcomes of biochemical disease-free survival, treatment-related morbidity and cardiovascular events were considered to be surrogate end points and therefore of lower importance. Health-related quality of life was also considered to be an important outcome but data was limited and different studies reported different domains of quality of life. As a result the data on quality of life did not provide a comprehensive view of this outcome and the GDG therefore agreed that it was of limited use.
Quality of the evidence	The quality of the evidence was very low to low as assessed by GRADE for both outcomes. The GDG noted that the studies were subject to a number of design limitations that render them at high or unknown risk of bias. They also noted that most of the studies did not analyse the patients according to the risk groups of interest to the GDG (low, intermediate, high and locally advanced) and because of variation in risk group definitions across the studies, it was not possible to conduct a meta-analysis according to risk group.
Trade-off between clinical benefits and harms	Significant differences were found consistently across most outcomes analysed. The GDG noted that the evidence had shown improved survival for patients receiving combination treatment. Whilst side effects were reported there was no evidence of increased treatment-related morbidity, cardiovascular adverse events or decreased quality of life as a result of combination treatment. The GDG considered that the survival benefits, particularly for patients with intermediate and high risk localised disease, outweighed the potential harms.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG, based on their clinical experience, was that recommending combination treatment would result in an increased use of radiotherapy resources but it was difficult to assess the extent of this increase. Equally, recommending combination treatment, was likely to reduce the requirement for the management of recurrent and metastatic disease.

Update 2014

Clinical question: What is the optimal duration of hormone therapy when combined with external beam radiotherapy?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all pre-specified outcomes is summarised in Table 49.

Overall survival

Five randomised controlled trials provided evidence on the overall survival of men receiving combined hormone therapy and external beam radiotherapy (EBRT) for prostate cancer. Four of these trials provided data which could be included in a meta-analysis, which found low quality evidence of similar overall survival of men treated with long-term (6-28 months) compared to short-term (3-4 months) neoadjuvant and concurrent hormone therapy (hazard ratio of 0.98; 95% CI 0.87-1.11).

The fifth trial provided moderate quality evidence of better overall survival in men treated with long-term (36 months) concurrent and adjuvant hormone therapy compared to those treated short-term (6 months). The hazard ratio of 1.42 (95% CI 1.09-1.84) suggests that if hormone therapy were continued after 6 months for a further 30 months, there would be an absolute increase in survival of 5.7% at 5 years, increasing overall survival from 79.1% to 84.8% (based on Bolla *et al*. 2005).

Disease-free survival

Very low quality evidence from two randomised controlled trials suggests uncertainty about the duration of hormone therapy and disease-free survival. In one trial (RTOG 92-02) comparing 4 versus 28 months neoadjuvant and adjuvant hormone therapy, the risk of disease recurrence was significantly lower in those receiving short-term therapy (HR 0.82 95% CI 0.73-0.91). However, the second trial (TROG 96-01), which compared 3 versus 6 months neoadjuvant and concurrent hormone therapy, found the risk of disease recurrence to be significantly lower in those receiving long-term therapy (HR 1.25 95% CI 1.02-1.54).

Metastases-free survival

Three studies provided moderate quality evidence which suggests that men receiving neoadjuvant and concomitant hormone therapy combined with EBRT are at greater risk of developing distant metastases with short-term therapy (3-4 months) than with long-term (6-28 months). Two of these studies provided data which could be included in a meta-analysis, which gave a hazard ratio of 1.66 (95% CI 1.34-2.06), suggesting that if hormone therapy were continued after 3 months for a further 3 months, there would be an absolute decrease in the number of patients developing metastases of 6.5% at 10 years, decreasing the proportion who develop metastases from 17.4% to 10.9% (based on Horwitz *et al*. 2008).

Biochemical disease-free survival

Low quality evidence from six RCTs suggests that men receiving neoadjuvant & adjuvant hormone therapy combined with EBRT have a greater likelihood of biochemical recurrence with short-term therapy (3-4 months) than with long-term (6-28 months). Five of these studies provided data which could beincluded in the meta-analysis, which gave a hazard ratio of 1.20 (95% CI 1.08-1.33), suggesting that if hormone therapy were continued after 3 months for a further 3 months, there would be an absolute decrease in the number of patients with biochemical recurrence of 6.6% at 10 years, decreasing the proportion who experience biochemical recurrence from 64.8% to 58.2% (based on Horwitz *et al*. 2008).

Update 2014

Cardiovascular adverse events

Low quality evidence from two RCTs suggests that cardiovascular events are less likely to occur in men treated with short-term (4 months) neoadjuvant and adjuvant hormone therapy combined with EBRT, than with long-term (28 months) therapy (RR 0.42 95% CI 0.06-2.82). The evidence suggests that for every 100 men treated with short- instead of long-term neoadjuvant and adjuvant hormone therapy when combined with EBRT, there will 58 fewer cardiovascular adverse events.

Health-related quality of life

Two trials reported moderate-quality evidence on quality of life using the QLQ-C30 tool. The EORTC trial found no significant difference between groups treated with 6 versus 30 months of concurrent and adjuvant hormone therapy for any of the function scales: global health status and quality of life, physical functioning, cognitive functioning, emotional functioning, role functioning, or social functioning ($p \geq 0.1$ for each). Of the symptom scales used, only insomnia ($p=0.006$) reached statistical significance. However, the TROG 03-04 trial found all outcomes within the functional domain of the EORTC QLQ-C30 tool to be significantly different at both 18 and 36 months (global, role, cognitive, social, emotional and physical). Within the symptoms domain, dyspnea and fatigue were found to be significantly different at both 18 and 36 months.

A number of ad hoc quality of life questions were also included by the EORTC authors, all of which were scored significantly lower by those treated with short-term (6-month) hormone therapy: hot flushes, enlarged nipples or breasts, swelling of legs, problems passing urine, reduced interest in sex, and reduced sexual activity.

The TROG 03-04 study also provided moderate quality evidence of no significant difference between 6 months and 18 months of neoadjuvant and concurrent ADT using the overall International Prostate Symptom Score (IPSS) at 18 or 36 months ($p<0.01$). However, there was a significant difference in the sexual activity and hormone-treatment-related symptoms domains of the PR-25 tool at both 18 and 36 months.

Update 2014

Table 49: GRADE profile: what is the optimal duration of hormone therapy when combined with external beam radiotherapy?

Quality assessment							No. of events / patients			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short duration hormone therapy	Long duration hormone therapy	Relative effect (95% CI)	Quality
Death from any cause (follow-up 6.4 to 11.3 years)										
Neoadjuvant & adjuvant hormone therapy (3-4 vs. 6-28 months)										
4[1-4]	RCT	No serious	Serious[8]	No serious	Serious[9]	None	493/1155 (42.7%)	453/1159 (39.1%)	HR 0.98 (0.87-1.11)	LOW
Concurrent adjuvant hormone therapy (6 vs. 36 months)										
1[5]	RCT	Serious[10]	No serious	No serious	No serious	None	132/483 (27.3%)	98/487 (20.1%)	HR 1.42 (1.09-1.85)	MODERATE
Disease recurrence (follow-up 11 years)										
Neoadjuvant & adjuvant hormone therapy (3-4 vs. 6-28 months)										
2[2-3]	RCT	Serious[11]	Serious[12]	Serious[13]	No serious	None	653/763 (85.6%)	571/758 (75.3%)	HR 0.90 (0.82-0.99)	VERY LOW
Metastases recurrence (follow-up 11 years)										
Neoadjuvant & adjuvant hormone therapy (3-4 vs. 6-28 months)										
3[2-3,7]	RCT	Serious[11]	No serious	No serious	No serious	None	167/763 (21.9%)	107/758 (14.1%)	HR 1.66 (1.34-2.06)	MODERATE
Biochemical relapse (follow-up 2.5 to 11.3 years)										
Neoadjuvant & adjuvant hormone therapy (3-4 vs. 6-28 months)										
6[1-4,6,7]	RCT	Serious[14]	Serious[8]	No serious	No serious	None	600/950 (63.2%)	474/942 (50.3%)	HR 1.20 (1.08-1.33)	LOW
Cardiovascular adverse events										
2[2,7]	RCT	No serious	No serious	No serious	Very serious[9]	None	1/871 (0.11%)	3/861 (0.35%)	RR 0.42 (0.06-2.82)	LOW
Health-related quality of life										

Quality assessment							No. of events / patients			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short duration hormone therapy	Long duration hormone therapy	Relative effect (95% CI)	Quality
2[5,15]	RCT	Serious[10]	No serious	No serious	No serious	None	Mixed tools and outcomes reported.			MODERATE

1 Armstrong et al. 2011 (ICORG); 2 Horwitz et al. 2008 (RTOG 92-02); 3 Denham et al. 2011 (TROG 96-01); 4 Alexander et al. 2011 (Crook 2004); 5 Bolla et al. 2009 (EORTC); 6 Laverdiere et al. 2004; 7 Zapatero et al. 2011 (GICOR DART 01); 15 Denham 2012 (RTOG 03-04).
8 Moderate heterogeneity present (I2=30-60%). 9 Very few total events seen and confidence intervals about the effect estimate are wide in a number of studies. 10 Inadequate concealment of treatment allocation, groups not comparable for treatment completion, and required sample size was not reached (study may not be statistically powerful enough to detect a true effect) in one study (EORTC); quasi-random scheme used in second study (RTOG 03-04). 11 Inadequate concealment of treatment allocation. 12 Considerable heterogeneity in study results (I2=92%). 13 Differences in the definition of disease recurrence present. 14 Treatment groups not comparable at baseline and inadequate concealment of treatment allocation in some studies.

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. Despite being a topic that is quite well suited to economic modelling, no further economic analysis was undertaken. This was primarily because other topics were considered to be of higher economic importance and were thus assigned to a higher priority for analysis. In addition, it was relatively straightforward to estimate the likely economic impact of the recommendation without undertaking economic modelling.

Update 2014

Cost-effectiveness evidence (2008)

The literature search on adjuvant therapy identified 1027 potentially relevant papers. Eight of these papers were obtained for appraisal, of which 5 contained relevant economic evaluations (Konski 2005; Konski 2006; Moeremans 2004; Neymark *et al*. 2001 and Samant 2003). None of the studies were performed from a UK National Health Service (NHS) perspective.

All of the studies evaluated the use of neoadjuvant and/or adjuvant hormonal therapy. Four of the 5 studies compared the use of hormonal therapy as an adjunct to radiotherapy. The choice of adjuvant therapy in the fifth study was described as 'standard care', but few further details of it were provided. None of the studies assessed the use of hormonal therapies as an adjunct to radical prostatectomy. All five studies appeared to base their economic evaluation on at least one randomised control trial (RCT). However, all 5 were different because they assessed the cost-effectiveness of different treatment regimens. For example, Konski *et al*. (2005) compared the use of hormonal therapy, 2 months prior to the initiation of radiotherapy and for the duration of treatment, to radiotherapy alone. Whereas Konski *et al*. (2006) compared the use of a similar hormonal regimen with hormonal therapy continuing for 2 years after radiotherapy had finished. The overall quality of the evaluations was judged to be good. No study reported a base case incremental cost-effectiveness ratio above £30,000 per life-year/QALY gained. Taking into account both the quality of the clinical evidence and the results of the cost-effectiveness analyses, there was considered to be at least reasonable evidence to support the economic value of hormonal therapies in this setting.

Recommendations	**Offer men with intermediate- and high-risk localised prostate cancer 6 months of androgen deprivation therapy given before, during or after radical external beam radiotherapy. [new 2014]** **Consider extending the period of androgen deprivation therapy to 3 years for men with high-risk localised prostate cancer and discuss the benefits and risks of this option with them. [new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of overall survival together with metastases-free survival and biochemical disease-free survival to be the most important to identifying the optimal duration of androgen deprivation therapy when combined with external beam radiotherapy, as they reflect the likelihood of a patient staying alive. The GDG also considered treatment related morbidity, in particular cardiovascular adverse events, to be an important outcome as androgen deprivation therapy is associated with morbidity which can be significant. The GDG noted that data on health-related quality of life were limited.
Quality of the evidence	The evidence for overall survival was low to moderate quality as assessed by GRADE. There was moderate quality evidence for metastases-free survival, cardiovascular adverse events and health-related quality of life and low quality evidence for biochemical disease-free survival. The GDG noted that there were a small number of events for some outcomes and also that the studies used lower-dose radiotherapy which is no longer common practice.

Update 2014

Trade-off between clinical benefits and harms	It was noted that the evidence had shown improved metastases free and biochemical disease-free survival with short-term androgen deprivation therapy (combined with external beam radiotherapy), in men with intermediate- and high-risk prostate cancer. This was balanced against an acceptable level of side effects. However the evidence was inconclusive as to the optimal time point to start androgen deprivation therapy (before, during or after radiotherapy). In addition it was not possible to recommend a particular dose of radiotherapy for men with locally advanced prostate cancer because the evidence base had used lower dose radiotherapy than in current clinical practice. It was also noted that there was an improvement in overall survival with long term androgen deprivation therapy compared to short term, in men with high-risk disease. Whilst a more serious side effect profile was demonstrated with such long-term androgen deprivation therapy, the GDG agreed that the survival benefits probably outweighed the potential harms. However, the potential harms were felt to be significant enough to warrant a robust discussion of these outcomes with individual patients.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG, based on their clinical experience, was that recommending short term androgen deprivation therapy for men with intermediate- and high-risk disease would potentially reduce costs because men with low-risk disease would no longer receive this treatment and it would also shorten the duration of hormone treatment for some men, compared with current practice. The GDG also agreed that recommending long-term androgen deprivation therapy in men with high-risk disease was already part of current clinical practice and therefore would not represent a change in cost.

Update 2014

6.2.12 Other adjuvant therapies

It has been postulated that bisphosphonates might delay or prevent the development of bone metastases in men with no detectable metastatic spread. Other agents such as denosumab and abiraterone are being investigated as adjuvant therapy for men with locally advanced prostate cancer.

Recommendation	**Do not offer bisphosphonates for the prevention of bone metastases in men with prostate cancer. [2008]**
Qualifying statement	There is good quality evidence from 1 RCT of a lack of clinical effect to make this recommendation. There is also evidence for a lack of cost-effectiveness.

Clinical evidence (2008)

A good quality placebo controlled randomised trial (Mason *et al*. 2007) examined clodronate for the prevention of bone metastases in men with localised or locally advanced prostate cancer. There was no significant difference in overall survival, symptomatic bone metastases or prostate cancer death between the treatment arms. Dose modifying adverse events were more likely in the clodronate group.

Cost-effectiveness evidence (2008)

The literature search on the use of bisphosphonates for the prevention of skeletal-related events (SREs) identified 153 potentially relevant papers. Thirteen of these papers were obtained for appraisal, of which 1 full economic evaluation was identified and reviewed (Reed *et al*. 2004). It examined 4 mg zoledronic acid (versus placebo), every 3 weeks, in men with

advanced-stage prostate cancer and a history of metastatic bone disease as a method of preventing SREs. It was a non-UK based cost-utility analysis that was performed from a health services perspective. Results were presented in 2000–2002 US$. The evaluation was considered to be a good quality analysis.

The analysis was based on a single RCT of 15-months duration; treatment costs and benefits were not extrapolated past this period. Approximately 650 patients were entered into the RCT, however only information relating to 360 was included in the economic evaluation (for which baseline details were not provided). Utility scores were calculated using the EQ-5D questionnaire, which were recorded every 3-months as part of the trial design. Resource use was also collected prospectively alongside the RCT.

The results from the analysis showed that patients receiving zoledronic acid experienced fewer hospital days than people receiving placebo, although this difference was not statistically significant at conventional levels (mean of 5.6 vs 8.0 days respectively; p = 0.20). The additional healthcare costs of providing zoledronic acid plus its administration was approximately $5,700. The baseline incremental cost-effectiveness ratio per additional QALY was approximately $160,000, although this varied considerably during the sensitivity analysis. Using $2=£1, translates to an ICER of approximately £80,000 per additional QALY. The authors concluded that the use of zoledronic acid for the prevention of SREs for people with metastatic prostate cancer was unlikely to be cost-effective, which appears to be a reasonable conclusion given the quality of the evidence.

6.2.13 Lymph node involvement

Men with locally advanced prostate cancer have a high-risk of pelvic lymph node spread. Improvements in radiological imaging may lead to better identification of spread to pelvic lymph nodes. Pathological lymph node staging may be used when deciding on the treatment of selected high-risk men. However it is not clear whether those with proven lymph node metastases benefit from radiotherapy to the pelvis and prostate or whether they should be treated with hormonal therapy alone.

Recommendation	**Clinical oncologists should consider pelvic radiotherapy in men with locally advanced prostate cancer who have a > 15% risk of pelvic lymph node involvement[n] and who are to receive neoadjuvant hormonal therapy and radical radiotherapy. [2008]**
Qualifying statement	This recommendation is based on evidence from one large, randomised trial.

Clinical evidence (2008)

The evidence comprises one large randomised trial (Lawton *et al*. 2005). This trial shows acceptable toxicity and a benefit in biochemical control, which might translate into a more clinically meaningful benefit with longer follow-up.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority, therefore no attempt has been made to review or summarise the relevant cost-effectiveness literature.

6.2.14 Post-operative radiotherapy

After radical prostatectomy, men with evidence of extracapsular spread have been offered post-operative radiotherapy in an attempt to prevent local recurrence. Radiotherapy may also

n Estimates using the Roach formula; %LN risk = 2/3 PSA + (10x [Gleason score – 6])

be offered to men with biochemical failure and no evidence of metastatic spread (see Chapter 5).

Recommendation	**Do not offer immediate post-operative radiotherapy after radical prostatectomy, even to men with margin-positive disease, other than in the context of a clinical trial. [2008]**
Qualifying statement	There are two randomised trials which have not shown any improvement in survival from immediate post operative radiotherapy.

Clinical evidence (2008)

Evidence about adjuvant radiotherapy comes from two randomised trials (Bolla *et al*. 2005; Thompson, Jr. *et al*. 2006). There was no significant effect of adjuvant radiotherapy on overall or disease specific survival, although follow-up in the Bolla trial is not yet long enough to establish survival outcomes. Biochemical failure and clinical failure were significantly less likely in men receiving adjuvant radiotherapy. Complications were significantly increased in those receiving adjuvant radiotherapy when compared to standard care.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

6.2.5 Other local therapies

6.2.5.1 Surgery

The progression-free and overall survival for men with pT3 disease is worse than those with pT2. Clinical or radiological evidence of T3 disease is usually a contraindication to radical surgery; however, men with T3 cancers are sometimes treated with radical prostatectomy. The appropriate extent of lymphadenectomy and its influence on survival is uncertain.

Research recommendations	**The role of radical surgery and extended lymphadenectomy as primary therapy for locally advanced prostate cancer should be studied in clinical trials. [2008]**

6.2.5.2 Cryotherapy and HIFU

Cryotherapy or HIFU are used in some centres for men with T2/3 disease as a primary treatment.

Recommendation	**Do not offer high-intensity focused ultrasound and cryotherapy to men with locally advanced prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions.[o] [2008]**
Qualifying statement	There is insufficient evidence of the clinical and cost effectiveness of cryotherapy and HIFU in comparison to established interventions to recommend their routine use.

o NICE interventional procedures guidance 118, 119 and 145 evaluated the safety and efficacy of cryotherapy and high intensity focused ultrasound for the treatment of prostate cancer. NICE clinical guidelines provide guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS. As there was a lack of evidence on quality of life benefits and long-term survival. these interventions are not recommended in this guideline.

Recommendations on the follow-up of men with localised prostate cancer can be found in Chapter 4. These recommendations also apply to men with locally advanced prostate cancer.

6.3 Systemic therapy alone

For some men with locally advanced prostate cancer, hormonal therapy will be the primary therapy (see Chapter 8 for more information on primary hormonal therapy).

6.4 References

2008

Bolla, M., van, P. H., Collette, L., van, C. P., Vekemans, K., Da, P. L., de Reijke, T. M., Verbaeys, A., Bosset, J. F., van, V. R., Marechal, J. M., Scalliet, P., Haustermans, K., Pierart, M. & European Organization for Research and Treatment of Cancer. (2005) Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet, 366: 572–578.

Konski, AE. al. (2005) Economic analysis of a phase III clinical trial evaluating the addition of total androgen suppression to radiation versus radiation alone for locally advanced prostate cancer (Radiation Therapy Oncology Group protocol 86–10) International Journal of Radiation Oncology, Biology, Physics 63(3): 788–794.

Konski, A *et al*. (2006) Long-term hormone therapy and radiation is cost-effective for patients with locally advanced prostate carcinoma. Cancer 106(1). 51–57.

Kumar, S., Shelley, M., Harrison, C., Coles, B., Wilt, T. & Mason, M. (2006). Neo-adjuvant and adjuvant hormone therapy for localised prostate cancer [protocol for a Cochrane review]. Cochrane Database of Systematic Reviews 2006 Issue 2 Chichester (UK): John Wiley & Sons, Ltd.

Lawton, C. A., DeSilvio, M., Roach, I. M., Uhl, V., Krisch, E. B., Seider, M. J., Rotman, M., Jones, C., Asbell, S. O., Valicenti, R. K., Han, B. H. & Thomas Jr, C. R. An Update of the Phase III Trial Comparing Whole-Pelvic (WP) to Prostate Only (PO) Radiotherapy Metastatic prostate cancer and Neoadjuvant to Adjuvant Total Androgen Suppression (TAS): Updated Analysis of RTOG 94-13. 47th Annual ASTRO Meeting. International Journal of Radiation Oncology, Biology, Physics 63, S19. 2005.

Mason, M. D., Sydes, M. R., Glaholm, J., Langley, R. E., Huddart, R. A., Sokal, M., Stott, M., Robinson, A. C., James, N. D.,

Parmar, M. K., Dearnaley, D. P. & Medical Research Council, P. R. (2007) Oral sodium clodronate for nonmetastatic prostate cancer–results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873). J Natl Cancer Inst, 99: 765–776.

Messing, E. M., Manola, J., Sarosdy, M., Wilding, G., Crawford, E. D. & Trump, D. (1999) Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med, 341: 1781–1788.

Reed, S.D., Radeva, J.I, *et al*. (2004). Cost-effectiveness of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer. Journal of Urology 171(4):1537-1542

Neymark, NI *et al*. (2001) Cost-effectiveness of the addition of early hormonal therapy in locally advanced prostate cancer: Results decisively determined by the cut-off time-point chosen for the analysis. European Journal of Cancer 37(14): 1768–1774.

Samant, RS. (2003) A cost-outcome analysis of long-term adjuvant goserelin in addition to radiotherapy for locally advanced prostate cancer. Seminars in Urologic Oncology. 21(3): 171–177.

Thompson, I. M., Jr., Tangen, C. M., Paradelo, J., Lucia, M. S., Miller, G., Troyer, D., Messing, E., Forman, J., Chin, J., Swanson, G., Canby-Hagino, E. & Crawford, E. D. (2006) Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA, 296: 2329–2335.

2014

Alexander A, Crook J, Jones S, *et al*. (2010). Is biochemical response more important than duration of neoadjuvant hormone therapy before radiotherapy for clinically localized prostate cancer? An analysis of the 3- versus 8-month randomized trial. International Journal of Radiation Oncology, Biology, Physics 76(1): 23-30.

Armstrong JG, Gillham CM, Dunne MT *et al*. (2011). A randomized trial (Irish clinical oncology research group 97-01) comparing short versus protracted neoadjuvant hormonal therapy before radiotherapy for localized prostate cancer. International Journal of Radiation Oncology, Biology, Physics 81(1): 35-45.

Bolla M, Van Tienhoven G, Warde P, *et al*. (2010). External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. The lancet oncology 11(11): 1066-73.

Bolla M, de Reijke TM, van Tienhoven G, *et al*. (2009). Duration of androgen suppression in the treatment of prostate cancer. New England Journal of Medicine 360(24): 2516-2527.

D'Amico AV, Manola JM, Loffredo M, *et al*. (2004). 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. JAMA : the journal of the American Medical Association 292(7): 821-7.

Denham JW, Steigler A, Lamb DS *et al*. (2011). Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. The lancet oncology 12(5): 451-459.

Denham JW, Wilcox C, Lamb DS, *et al*. (2012). Rectal and urinary dysfunction in the TROG 03.04 RADAR trial for locally advanced prostate cancer. Radiotherapy and Oncology 105: 184-192.

Efstathiou JA, Bae K, Shipley WU, *et al*. (2007). Obesity and mortality in men with locally advanced prostate cancer: analysis of RTOG 85-31. Cancer 110(12): 2691-9.

Efstathiou JA, Bae K, Shipley WU, *et al*. (2009). Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. Journal of Clinical Oncology 27(1): 92-9.

Fellows GJ, Clark PB, Beynon LL, *et al*. (1992). Treatment of advanced localized prostatic cancer by orchiectomy, radiotherapy or combined treatment. British Journal of Urology 70: 304-9.

Granfors T, Modig H, Damber JE, *et al*. (2006). Long-term followup of a randomized study of locally advanced prostate cancer treated with combined orchiectomy and external radiotherapy versus radiotherapy alone. Journal of Urology 176: 544-547.

Update 2014

Horwitz EM, Bae K, Hanks GE *et al*. (2008). Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26(15): 2497-2504.

Jones CU, Hunt D, McGowan DG, *et al*. (2011). Radiotherapy and short-term androgen deprivation for localized prostate cancer. The New England journal of medicine 365(2): 107-18.

Laverdiere J, Nabid A, De Bedoya LD, *et al*. (2004). The efficacy and sequencing of a short course of androgen suppression on freedom from biochemical failure when administered with radiation therapy for T2-T3 prostate cancer. Journal of Urology 171(3): 1137–1140.

Mottet N (2010). Radiotherapy combined with androgen deprivation vs androgen deprivation alone in clinically locally advanced prostate cancer (PCA) T3-T4,N0,M0 in a multicenter randomised phase III study. Journal of Urology Conference(var.pagings):4.

Pilepich MV, Winter K, Lawton CA, *et al*. (2005). Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma-Long-term results of phase III RTOG 85-31. International Journal of Radiation Oncology, Biology, Physics 61: 1285-90.

Roach M, Bae K, Speight J, *et al*. (2008). Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. Journal of clinical oncology 26(4): 585-91.

See WA and Tyrrell CJ, (2006). The addition of bicalutamide 150 mg to radiotherapy significantly improves overall survival in men with locally advanced prostate cancer. Journal of Cancer Research & Clinical Oncology 132 (Suppl 1): S7-16.

Warde PR, Mason MD, Sydes MR, *et al*. (2010). Intergroup randomized phase III study of androgen deprivation therapy (ADT) plus radiation therapy (RT) in locally advanced prostate cancer (CaP) (NCIC-CTG, SWOG, MRC-UK, INT: T94-0110; NCT00002633) [abstract no.CRA4504]. Journal of Clinical Oncology 28: 959.

Widmark A, Klepp O, Solberg A, *et al*. (2009). Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. [Erratum appears in Lancet 373(9670): 1174]. Lancet 373(9660): 301-8.

Zagars GK, Johnson DE, Eschenbach ACv, *et al*. (1988). Adjuvant estrogen following radiation therapy for stage C adenocarcinoma of the prostate: Long-term results of a prospective randomized study. International Journal of Radiation Oncology, Biology, Physics 14: 1085-91.

Zapatero A, Guerrero A, Maldonado X, *et al*. (2011). Phase III trial comparing long-term versus short-term androgen deprivation combined with high-dose radiotherapy for localized prostate cancer: GICOR protocol DART 01/05. ASCO Annual Meeting Proceedings Conference Poster; 29 (15): 4580.

Update 2014

7 Hormone therapy

7.1 Introduction

The function of hormone therapy is to stop testosterone feeding prostate cancer and encouraging growth. Treatment is long-term, usually continuous and is often for several years.

There are two main methods of achieving control of prostate cancer by hormonal manipulation: (i) androgen deprivation (using luteinising hormone-releasing hormone agonists (LHRHa) or bilateral orchidectomy), which removes the supply of endogenous hormone; or (ii) androgen receptor blockade (anti-androgens), which reduces the effect of endogenous hormones. Both forms of therapy have proven efficacy for different states of the disease. Each method has associated morbidity and potentially specific impacts on the individual's quality of life.

7.2 Neoadjuvant and adjuvant hormone therapy

Recommendations on neoadjuvant and adjuvant hormone therapy can be found in section 6.2.1.

7.3 Hormone therapy in metastatic disease

Recommendations on hormone therapy in metastatic disease can be found in sections 8.2 – 8.5.

Uncertainty exists as to whether continuous hormone treatment is always required; if intermittent hormone therapy was at least as effective at controlling prostate cancer the side-effects might be less. However, despite this, there is concern about stopping continuous treatment for fear of a detrimental effect and allowing disease progression.

Update 2014

Clinical question: Is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all pre-specified outcomes is summarised in Table 50.

Overall survival

Moderate quality evidence from six randomised trials shows no significant difference in overall survival between men treated with intermittent hormone therapy and those treated with continuous hormone therapy (p=0.17; only five included in meta-analysis).

Progression-free survival (not biochemical)

Low quality evidence from two randomised trials found no significant difference in progression-free survival between intermittent and continuous therapy. However, both trials included both clinical and biochemical progression in their definition of disease progression. Three studies also provided very low quality evidence of no significant difference in progression-free survival between intermittent and continuous treatment groups for clinical progression.

Adverse events

One moderate quality study found the incidence of treatment-emergent adverse events to be borderline significantly higher in the continuous treatment group (p=0.042) (Mottet *et al*. 2009). However, two further studies provided low quality evidence of no significant difference in the rates of adverse events between groups but provided no figures. Crook (2011) also reported no significant difference between treatment arms in the rate of cardiovascular events or osteoporotic fractures (but did not provide figures). While Hering *et al*. (2000) observed fewer mild adverse events (gastrointestinal, gynaecomastia and fatigue) and severe adverse events (severe nausea/vomiting and oedema of the lower limb) with intermittent than with continuous therapy (RR 0.29 and 0.15 respectively).

Low quality evidence from two randomised trials suggests that hot flushes are significantly less likely with intermittent than with continuous hormone therapy. While both studies reported fewer hot flushes with intermittent therapy (RR 0.66 and 0.97 respectively) there is uncertainty about the size of the effect due to heterogeneity.

Moderate quality evidence from one randomised trial (Calais da Silva *et al*. 2009) shows gynaecomastia is less likely in men treated with intermittent than with continuous hormone therapy (RR 0.64 95% CI 0.43-0.93). The evidence suggests that for every 100 men treated with intermittent instead of continuous therapy there would be seven fewer cases of gynaecomastia. Crook (2011) also reported patients receiving intermittent had significantly less gynaecomastia than those receiving continuous therapy but no effect size was reported (p<0.001).

Low quality evidence from one randomised trial (Calais da Silva *et al*. 2009) suggests sexual activity within the previous month was more likely during intermittent therapy than during continuous therapy (RR 2.90 95% CI 1.52-5.53). The evidence suggests for every 100 men treated with intermittent instead of continuous therapy there would be an additional 18 reporting sexual activity within the previous month. Low quality evidence from another randomised trial (Hering *et al*. 2000) found impotence was much less likely in men receiving intermittent than in those on continuous therapy (RR 0.06 95% CI 0.01-0.28). While Crook (2011) reported that patients receiving intermittent had significantly greater desire for sexual activity and better erectile function than those receiving continuous therapy but no effect sizes reported (p<0.001). Miller *et al*. (2007) also found self-assessed sexual activity to be better with intermittent therapy (but no effect sizes were reported).

Update 2014

Health-related quality of life

Very low quality evidence from five randomised trials suggests better quality of life with intermittent than with continuous therapy. The studies reported that patients receiving intermittet therapy had significantly better physical function (p<0.001), overall self-assessed health (p<0.001), and physical and emotional scores, but did not report the actual figures. However, one moderate quality study did not find any significant difference between the treatment groups using the QLQ-C30 but did not provide figures (Mottet *et al*. 2009).

Another study found that those in the intermittent group were significantly less likely to report impotence (p<0.001) or poor mental health (p=0.003) at 3 months (Hussain *et al*. 2013). At 9 months patients in the intermittent group were more likely to report high libido (p=0.01) and less likely to report impotence (p<0.001). However, at 15 months there remained no significant difference between groups in any of the quality of life outcomes. While Salonen *et al*. (2013) found significant differences in sexual functioning but not activity limitation or physical capacity, favouring intermittent treatment at a median follow-up of 65 months, but did not report individual scores or outcomes of other domains.

Treatment-related morbidity and mortality, patient acceptability

These outcomes were not reported by any of the included studies.

Table 50: GRADE profile: is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer?

Quality assessment							Number of events		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intermittent HT	Continuous HT	Relative risk	95% CI	Absolute	
Death from any cause												
5	RCTs	Serious[1]	None	None	None	None	1176 / 2048 (57.4%)	1142 / 2053 (55.6%)	HR 1.06	0.98 – 1.15	21 more per 1,000 (from 7 fewer to 51 more)	MODERATE
Disease progression												
2	RCTs	Serious[2]	None	Serious[3]	None[2]	None	- / 588	- / 592	HR 1.13	0.97 – 1.31	Not estimable	LOW
Treatment-related mortality												
0	-	-	-	-	-	-	-	-	-	-	-	-
Patient acceptability												
0	-	-	-	-	-	-	-	-	-	-	-	-
All adverse events												
1	RCT	Serious[11]	None	None	None	None	81 / 96 (84.4%)	88 / 94 (93.6%)	RR 0.90	0.81 – 1.00	94 fewer per 1,000 (from 178 fewer to 0 more)	MODERATE
Hot flushes												
2	RCTs	Serious[1]	Serious[4]	None	Serious	None	680 / 989 (68.8%)	735 / 989 (74.3%)	RR ranged from 0.66 to 0.97		-	VERY LOW
Gynaecomastia												
1	RCT	Serious5	None	None	None	None	37 / 299 (12.4%)	57 / 293 (19.5%)	RR 0.64	0.43 – 0.93	70 fewer per 1000 (from 14 fewer to 111 fewer)	MODERATE

Quality assessment							Number of events		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intermittent HT	Continuous HT	Relative risk	95% CI	Absolute	
Sexual activity within the previous month												
1	RCT	Serious[5]	None	None	None	None	39 / 140 (27.9%)	10 / 104 (9.6%)	RR 2.9	1.52 – 5.53	183 more per 1000 (from 50 more to 436 more)	MODERATE
Impotence												
1	RCT	Serious[5]	None	None	Serious[6]	None	1 / 25 (4%)	18 / 18 (100%)	RR 0.06	0.01 – 0.28	940 fewer per 1000 (from 720 fewer to 990 fewer)	LOW
Health-related quality of life												
5	RCTs	Serious[7]	Serious[7]	None	Serious[7]	None	-	-	Not pooled		Not pooled	VERY LOW

1 Unclear allocation concealment and random sequence generation. Selective outcome reporting in Salonen 2013.
2 One trial published in abstract only - very limited information about study conduct and about trial outcomes.
3 Disease progression included both objective subjective progression in Calais 2009.
4 Heterogeneity in effect sizes. The control group rate of hot flashes was markedly different between studies.
5 Unclear allocation concealment and random sequence generation.
6 Low number of events
7 Two of the studies were published in abstract form only, unclear study conduct and no reporting of effect sizes.
8Unclear allocation, randomisation schedule, or blinding. Analysis was not intention-to-treat in one study.
9Continuous treatment arm received i ntermittent therapy with start and stop critieria of PSA > 0.1 ng/ml and < 0.1 ng/ml respectively; but received continuous finasteride in Dutkiewicz 2012.
10Less than 50 events for clinical progression. Less than 150 events for biochemical progresssion.
11 Unclear allocation, randomisation schedule

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. No further economic modelling was undertaken for this topic as it was not thought to be necessary because estimating the likely economic effects of the recommendation seemed relatively straightforward. Thus, other topics with more complex cost and benefit trade offs were prioritised for economic modelling.

Recommendation	**Consider intermittent therapy for men having long-term androgen deprivation therapy (not in the adjuvant setting), and include discussion with the man, and his family or carers if he wishes, about:** • **the rationale for intermittent therapy and** • **the limited evidence for reduction in side effects from intermittent therapy and** • **the effect of intermittent therapy on progression of prostate cancer.** **[new 2014]** **For men who are having intermittent androgen deprivation therapy:** • **measure PSA every 3 months and** • **restart androgen deprivation therapy if PSA is 10 ng/ml or above, or if there is symptomatic progression.** **[new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of overall survival, progression free survival and reduction in adverse events to be the most important as these would indicate the effect of intermittent hormone therapy on both survival and quality of life. Patient acceptability and treatment-related morbidity were also considered important outcomes but were not reported by the evidence.
Quality of the evidence	The evidence for this question was assessed by GRADE as being very low quality for health-related quality of life and progression free survival, low to moderate quality for reduction in adverse events and moderate quality for overall survival. The GDG noted that many of the included studies were only available in abstract form. However the data reported in these abstracts was consistent with that reported in full papers and so the GDG agreed it was appropriate to include these abstracts in the evidence base
Trade-off between clinical benefits and harms	The GDG noted that the evidence had shown no difference in overall survival between intermittent and continuous hormone therapy. Also that intermittent hormone therapy had been associated with improvements in health-related quality of life and reduction in adverse events which could potentially lead to improved patient acceptability. However it was noted that this evidence was of very low to moderate quality. The GDG also acknowledged, based on their clinical experience, that it was possible for men receiving intermittent hormone therapy to be lost to follow-up and potentially undertreated. Nonetheless the GDG agreed that the potential benefits of receiving intermittent hormone therapy outweighed the harms.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG, based on their clinical experience, was that recommending intermittent hormone therapy, instead of continuous, would result in cost savings. However there would likely be additional costs associated with the requirement for increased PSA testing in follow-up. The GDG were unclear what the net effect of this would be.
Other considerations	The GDG noted that clarification was needed on which men could be considered for intermittent hormone therapy – to avoid the potential for variation in practice. They agreed to recommend this treatment for those

Update 2014

	men maintaining a PSA <10, as this was the PSA level consistently reported in the studies that had been appraised. The GDG were also concerned that regular PSA monitoring, which was part of the trial protocols for intermittent hormone therapy, may not happen outside of the trial setting. They therefore agreed to recommend 3 monthly PSA monitoring as this was the maximum interval reported in the trials that comprised the evidence base for this topic.

Signalling through the androgen receptor remains critically important in hormone relapsed prostate cancer and several new drugs have been designed to disrupt this pathway. Recommendations on 'Prostate cancer (metastatic, castration resistant) - abiraterone (following cytoxic therapy)' can be found in NICE technology appraisal guidance 259.

7.4 Managing the complications of hormone therapy

Androgen deprivation decreases a mans testosterone levels over the long term, which can lead to adverse effects, including cardiovascular morbidity/mortality, hot flushes, sexual dysfunction, osteoporosis and fatigue.

Anti-androgen therapy is less likely to result in sexual dysfunction and/or lethargy. These agents however commonly cause breast enlargement (gynaecomastia) and breast pain (mastalgia).

7.4.1 Cardiovascular effects

It has been postulated that long term decrease in testosterone levels may lead to an increased risk of cardiovascular morbidity (including thromboembolic events and myocardial infarction) and mortality.

Update 2014

Clinical question: What are the adverse cardiovascular effects of long-term androgen deprivation and how prevalent are they?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all pre-specified outcomes is summarised in Tables 51 to 55.

Cardiovascular mortality

Eleven studies provided low quality evidence on cardiovascular mortality in patients receiving androgen deprivation therapy (ADT), though these varied in their definitions and results. The adjusted hazard ratios of receiving any ADT compared to a control without ADT ranged from 0.96 to 1.70. Adjusted hazard ratios for receiving ADT and radiotherapy compared to radiotherapy alone ranged from 0.7 to 1.2 and those for patients receiving both ADT and prostatectomy compared to prostatectomy alone ranged from 1.3 to 2.6. The standardised mortality ratio (SMR) for patients who received any form of ADT ranged from 0.38 to 1.29 in the studies. Only seven of the studies provided data in a format which could be included in a meta-analysis; this found no statistically significant difference in risk (RR 1.37 95% CI 0.90-2.07).

The sub-group analyses involving five studies showed no significant difference between patients receiving LHRH agonists alone or with anti-androgens and those receiving no ADT ($p>0.05$). In three of these studies ADT was given alongside radiotherapy. One study (McLeod *et al*. 2006) showed a borderline significant difference between those receiving anti-androgens and standard care (radical therapy or watchful waiting) compared to those

receiving standard care alone (RR 1.3 95% CI 1.0-1.6). Another study (van Hemelrijck *et al*. 2010a) provided very low quality evidence of significantly fewer deaths due to myocardial infarction, arrthymia, ischemic heart disease (IHD), and heart failure in patients receiving anti-androgen monotherapy compared to other medical ADT (RRs: 0.57, 0.36, 0.54, and 0.26 respectively). The results suggest that for every 1,000 patients treated with anti-androgen monotherapy instead of another type or combined ADT, there would be 17 fewer deaths from myocardial infarction, four fewer from arrthymia, 32 fewer from IHD, and ten fewer from heart failure. No combined measure of cardiovascular mortality was reported by ADT type.

Following restriction of the meta-analysis to studies involving ≥ 6 months ADT, there remained no significant increase in the incidence of cardiovascular deaths between patients treated with ≥ 6 months of ADT and patients receiving no ADT, based on very low quality evidence from two studies. In a very low quality study not included in the meta-analysis Kim *et al*. (2011) found that incidence of cardiovascular death at 7 years was significantly higher at 1.4% in patients receiving > 6 months of ADT alongside EBRT, compared to 2.6% in patients receiving EBRT alone (p=0.001). Another low quality study by Alibhai *et al*. (2009) found that patients receiving > 24 months of ADT had a significantly lower risk of sudden cardiac death compared to patients receiving < 3 months (RR 0.81 95% CI 0.69-0.96), but patients receiving 3-6 months or 6-24 months ADT did not. In a moderate quality study D'Amico *et al*. (2007) reported that men aged ≥ 65 years who received 6 months of ADT experienced a shorter time to fatal myocardial infarction than men of the same age group who did not receive ADT (p=0.017). However, in their second study no significant difference in time to fatal myocardial infarction was found between patients aged ≥ 65 years receiving 6-8 months of ADT compared to patients receiving 3 months.

Upon exclusion of the only study reporting exclusion of patients with comorbidities (Tsai *et al*. 2007) from the meta-analysis, there remained no significant difference in cardiovascular mortality between patients receiving ADT and those not. The very low quality study which was excluded found a significant increase in cardiovascular mortality in patients receiving ADT compared to patients not receiving ADT. The relative risk of 2.44 (95% CI 1.73-3.44) suggests that for every 1,000 patients without comorbidities, treated with ADT, there would be 28 more cardiovascular deaths.

Update 2014

Four RCTs or analyses of multiple RCTs were included in a sub-group meta-analysis; there remained no significant difference in incidence of cardiovascular mortality between patients receiving ADT and those not. A sub-group analysis of the cohort studies provided very low quality evidence of a significant increase in risk in patients receiving ADT (RR 2.15 95% CI 1.33-3.46), suggesting that for every 1,000 patients there are 23 more cardiovascular deaths in patients treated with ADT.

Cardiovascular morbidity

Six studies provided very low quality evidence of cardiovascular morbidity in patients receiving hormone therapy. The studies varied in the type of events reported, with five reporting incidence of myocardial infarction, three reporting the incidence of coronary heart disease, two the incidence of heart failure, and one the incidence of arrhythmia. The incidence rate ranged widely between studies; between 10.2 and 61.3 cases per 1,000 person-years in those receiving hormone therapy, compared to between 7.4 and 29.7 per 1,000 person-years in the no-hormone therapy group. Studies also varied in whether the risk of cardiovascular disease was found to be lower in the hormone therapy or no-hormone therapy group, with the hazard ratio varying between 0.92 and 1.98. One study (van Hemelrijck 2010a and 2010b) reported the SIR which was found to range between 1.12 and 1.47. Only two studies provided data which could be included in the meta-analysis, which found no significant difference in risk between those that received hormone therapy and those that did not.

One study provided very low quality evidence of significantly fewer overall cases of myocardial infarction, ischemic heart disease (IHD), and heart failure with anti-androgen monotherapy compared to other types of ADT (RRs: 0.79, 0.85, 0.54, and 0.85 respectively) (van Hemelrijck *et al*. 2010a). The results suggest that for every 1,000 patients treated with anti-androgen monotherapy instead of another or combined type of ADT, there would be 14 fewer cases of myocardial infarction, 15 fewer cases of IHD, and 33 fewer cases of heart failure. There was no significant difference in the risk of developing arrthymia for patients receiving anti-androgen monotherapy compared with any other type of ADT.

One study (Alibhai *et al*. 2009) provided low quality evidence of a borderline significant difference in the incidence of myocardial infarction between patients receiving ≥ 6 months ADT and patients receiving no ADT. The relative risk of 0.87 (95% CI 0.80-0.95) suggests that for every 1,000 patients treated with ≥ 6 months ADT there will be seven fewer myocardial infarctions. However, in their multivariate model Alibhai *et al*. (2009) found no significant difference in the risk of myocardial infarction for patients receiving 3-6 months, 6-24 months, or > 24 months ADT compared to patients receiving < 3 months. Alibhai *et al*. (2009) did find a significant difference in the incidence of congestive heart failure between patients treated with ≥ 6 months of ADT compared to patients receiving no ADT. The relative risk of 0.92 (95% CI 0.87-0.97) suggests that for every 1,000 patients 10 fewer would develop congestive heart failure if treated with ≥ 6 months of ADT. The multivariate model suggests that this different was only significant for the subgroup receiving > 24 months ADT (HR 0.81 95% CI 0.69-0.96) and not for the 3-6 or 6-24 month-subgroups.

None of the studies reported restricting their patients by comorbidities criteria. Three cohort studies reported on the incidence of cardiovascular events and found no significant difference between groups.

Cerebrovascular accident mortality

Two studies provided very low quality evidence of no significant increase in deaths from stroke in patients treated with hormone therapy compared to a control. A cohort study by van Hemelrijck *et al*. (2010a) found the SMR to range between 0.81 and 1.24 for different hormone therapies, compared to 0.99 and 1.01 for the curative therapy and surveillance control groups.

Following restriction of the meta-analysis to anti-androgen monotherapy versus no ADT there remained no statistically significant difference in the incidence of death due to stroke. One study (van Hemelrijck *et al*. 2010a) provided very low quality evidence of significantly fewer deaths due to stroke in patients receiving anti-androgen monotherapy compared to other medical ADT (RR 0.56 95% CI 0.40-0.79). The results suggest that for every 1,000 patients treated with anti-androgen monotherapy instead of another type or combined ADT, there would be eight fewer deaths from stroke.

Following restriction of the meta-analysis to studies involving ≥ 6 months ADT, there remained no significant increase in the incidence of deaths due to stroke between patients treated with ≥ 6 months of ADT and patients receiving no ADT, based on very low quality evidence from two studies.

None of the studies reported restricting their patients by comorbidities criteria. Only one RCT (McLeod *et al*. 2006) reported the incidence of deaths due to stroke and found no significant difference between patients treated with ADT and those not.

Cerebrovascular accident morbidity

Five studies provided very low quality evidence on incidence of stroke in patients treated with hormone therapy. The incidence rate ranged widely between studies; between 14.7 and 34.7 cases per 1,000 person-years in those receiving hormone therapy, compared to between 11.3 and 12 per 1,000 person-years in the no-hormone therapy group. One study reported

Update 2014

incidence rates between 14.7 and 34.7 per 1,000 person-years in different hormone therapy sub-groups, compared with 11.3 per 1,000 person-years in the no-hormone therapy group (Keating *et al*. 2010). The adjusted hazard ratios reported for the hormone therapy group varied between 0.88 and 1.81 with studies results varying as to whether the risk was higher or lower in those treated with hormone therapy. Van Hemelrijck *et al*. (2010a) found the SIRs to range from 1.19 to 1.36 for the different hormone therapies, compared to 0.98 and 1.19 for the curative therapy and surveillance groups. Three of the studies provided data which could be included in a meta-analysis, which found no significant difference in risk between those that received hormone therapy and those that did not.

Following restriction of the meta-analysis to anti-androgen monotherapy versus no ADT there remained no statistically significant difference in the incidence of stroke. One study provided very low quality evidence of significantly fewer overall cases of stroke with anti-androgen monotherapy compared to other types of ADT (OR 0.85 95% CI 0.75-0.96) (van Hemelrijck *et al*. 2010a). The results suggest that for every 1,000 patients treated with anti-androgen monotherapy instead of another or combined type of ADT, there would be 12 fewer cases of stroke.

When the meta-analysis was restricted to studies comparing ≥ 6 months ADT with no ADT, only one study (Alibhai *et al*. 2009) providing low quality evidence was included. This study found a significant difference in the incidence of stroke between patients treated with ≥ 6 months of ADT compared to patients receiving no ADT (RR 0.84 95% CI 0.78-0.91), suggesting that for every 1,000 patients 10 fewer would have a stroke if treated with ≥ 6 months of ADT.

Upon exclusion of the only study reporting exclusion of patients with comorbidities (Chung *et al*. 2012) from the meta-analysis, there remained no significant difference in the incidence of stroke between patients receiving ADT and those not. The very low quality excluded study found no significant difference in the incidence of stroke between patients receiving ADT and those not receiving ADT.

Four cohort studies reported on the incidence of stroke and found no significant difference between groups.

Update 2014

Thromboembolic events

Three studies provided very low quality evidence of the incidence of thromboembolic events in patients receiving hormone therapy. Two of these studies included any thromboembolic event, however their definitions varied. The third study (Hu *et al*. 2012) reported only the number of cases of deep venous thrombosis seen. The reported incidence rate ranged from 13.2 to 14.7 per 1,000 person years for patients receiving hormone therapy compared to 10.1 cases per 1,000 person-years in the no-hormone therapy group (where reported). The adjusted hazard ratio ranged from 1.10 to 1.56, suggesting an increased risk in patients receiving hormone therapy. The SIRs ranged from 1.56 to 2.81, also suggesting more cases than would be expected. However, where surveillance or curative therapy was used as a comparator, the SIRs ranged from 1.27 to 1.57 and from 1.73 to 2.03 respectively suggesting that these groups also saw more cases than expected.

One study provided very low quality evidence of significantly fewer overall cases of deep venous thrombosis and pulmonary embolism (RRs: 0.54 and 0.67 respectively) (van Hemelrijck *et al*. 2010b). The results suggest that for every 1,000 patients treated with anti-androgen monotherapy instead of another or combined type of ADT, there would be seven fewer cases of DVT and four fewer cases of pulmonary embolism.

No studies reporting thromboembolic events compared ≥ 6 months ADT with no ADT. However, a very low quality study by Ehdaie *et al*. (2012) found that risk of thromboembolic event was increased by 40% (95% CI 1.33-1.45) in patients receiving < 1 year of ADT, by 66% (95% CI 1.57-1.75) in patients receiving 1-3 years of ADT, and doubled in patients

receiving > 3 years of ADT (95% CI 1.90-2.19) compared to patients receiving no ADT. Another low quality study (Hu *et al*. 2012) undertook subgroup analyses and found incidence of DVT to be significantly higher in patients receiving > 12 months of ADT compared to no ADT (HR 1.23 95% CI 1.11-1.36 for 13-24 months and HR 1.15 95% CI 1.04-1.27 for >25 months duration) but not for patients receiving ≤ 12 months of ADT.

None of the studies reported restricting their patients by comorbidities criteria. Two cohort studies reported on the incidence of thromboembolic events and found no significant difference between patients treated with ADT and those not.

Update 2014

Table 51: GRADE profile: what are the adverse cardiovascular effects of long-term androgen deprivation and how prevalent are they?

Quality assessment							Number of events		Effect		
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADT	No ADT	Relative risk	95% CI	Quality
Death from cardiovascular disease (median follow-up 3.8 – 8.1 years)											
11 (7)	6 cohort & 5 RCTs	Serious[1]	Serious[2]	None	Serious[4]	None	453 / 8642	454 / 15117	1.37	0.90 – 2.07	LOW
Death from cerebrovascular accident (median follow-up 4.0 - 7.4 years)											
2 (2)	1 cohort & 1 RCT	Serious[1]	None	None	Serious[3]	None	593 / 34664	471 / 49989	1.46	0.81 – 2.65	VERY LOW
Cardiovascular disease (median 2.6 – 6.5)											
6 (3)	Cohort studies	Serious[1]	Serious[2]	None	Serious[4]	None	8026 / 60985	7173 / 81556	1.29	0.78 – 2.16	VERY LOW
Cerebrovascular accident (median 2.6 – 6.5 years)											
5 (4)	Cohort studies	Serious[1]	Serious[2]	None	None	None	4012 / 61049	4650 / 81857	1.10	0.84 – 1.42	VERY LOW
Thromboembolic events (median 4.3 – 5.1 years)											
3 (2)	Cohort studies	Serious[1]	Serious[2]	None	Serious[4]	None	9620 / 89108	9403 / 138315	0.99	0.24 – 4.13	VERY LOW

**Figures in brackets are the number of studies which provided the number of cases and were incorporated into the meta-analysis. 1 Includes studies with follow-up < 5 years. 2 Wide variation in relative risk where reported/calculated. 3 Total number of events is < 300 (where reported). 4 Wide confidence intervals calculated for relative risk.*

Table 52: GRADE profile: what are the adverse cardiovascular effects of long-term androgen deprivation and how prevalent are they? Sub-group analyses: anti-androgen monotherapy versus other androgen deprivation therapy (ADT)

Quality assessment							Number of events		Relative effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-androgen monotherapy	Other ADT	RR	95% CI	Absolute effect	Quality
Myocardial infarction mortality (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	80 / 3391 (2.4%)	1083 / 26052 (4.2%)	0.57	0.45 – 0.71	17 fewer per 1,000 (from 12 fewer to 22 fewer)	VERY LOW
Arrthymia mortality (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	8 / 3391 (0.2%)	173 / 26052 (0.7%)	0.36	0.18 – 0.72	4 fewer per 1,000 (from 2 fewer to 5 fewer)	VERY LOW
Ischemic heart disease mortality (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	135 / 3391 (4.0%)	1913 / 26052 (7.3%)	0.54	0.46 – 0.64	32 fewer per 1,000 (from 25 fewer to 38 fewer)	VERY LOW
Heart failure mortality (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	12 / 3391 (0.4%)	354 / 26052 (1.4%)	0.26	0.15 – 0.46	10 fewer per 1,000 (from 7 fewer to 12 fewer)	VERY LOW
Stroke mortality (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	36 / 3391 (1.1%)	492 / 26052 (1.9%)	0.56	0.40 – 0.79	8 fewer per 1,000 (from 4 fewer to 11 fewer)	VERY LOW
Myocardial infarction morbidity (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	189 / 3391 (5.6%)	1839 / 26052 (7.1%)	0.79	0.68 – 0.91	14 fewer per 1,000 (from 6 fewer to 21 fewer)	VERY LOW
Arrthymia morbidity (mean follow-up 4 years)												
1	Cohort	Serious	None	None	None	None	195 / 3391	1438 /	1.04	0.90 –	2 more per 1,000	VERY

Quality assessment							Number of events		Relative effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-androgen monotherapy	Other ADT	RR	95% CI	Absolute effect	Quality
		[1]					(5.8%)	26052 (5.5%)		1.20	(from 5 fewer to 10 more)	LOW
Ischemic heart disease morbidity (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	316 / 3391 (9.3%)	2861 / 26052 (11.0%)	0.85	0.76 – 0.95	15 fewer per 1,000 (from 5 fewer to 24 fewer)	VERY LOW
Heart failure morbidity (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	136 / 3391 (4.0%)	1941 / 26052 (7.5%)	0.54	0.45 – 0.64	33 fewer per 1,000 (from 26 fewer to 40 fewer)	VERY LOW
Stroke morbidity (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	252 / 3391 (7.4%)	2283 / 26052 (8.8%)	0.85	0.75 – 0.96	12 fewer per 1,000 (from 3 fewer to 20 fewer)	VERY LOW
Deep venous thrombosis (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	27 / 3391 (0.8%)	386 / 26052 (1.5%)	0.54	0.36 – 0.79	7 fewer per 1,000 (from 3 fewer to 9 fewer)	VERY LOW
Pulmonary embolism (mean follow-up 4 years)												
1	Cohort	Serious [1]	None	None	None	None	29 / 3391 (0.9%)	332 / 26052 (1.3%)	0.67	0.46 – 0.98	4 fewer per 1,000 (from 0 fewer to 7 fewer)	VERY LOW

1 Inadequately short follow-up (van Hemelrjick 2010).

Table 53: GRADE profile: what are the adverse cardiovascular effects of long-term androgen deprivation and how prevalent are they? Sub-group analyses: androgen deprivation therapy (ADT) of duration ≥ 6 months versus no ADT

Quality assessment							Number of events		Relative effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADT duration ≥ 6 months	No ADT	RR	95% CI	Absolute effect	Quality
Cardiovascular mortality (median follow-up 5.4-8.1 years)												
2	1 cohort & 1 RCT	None	None	Serious[1]	Serious[2,3]	None	59 / 582 (10.1%)	92 / 1024 (9.0%)	0.92	0.56 – 1.50	7 fewer per 1,000 (from 40 fewer to 45 more)	VERY LOW
Cerebrovascular accident mortality (median follow-up 5.4 years)												
1	Cohort	None	None	Serious[1]	Serious[2]	None	0 / 105 (0.0%)	3 / 556 (0.5%)	0.75	0.04 – 14.43	1 fewer per 1,000 (from 5 fewer to 67 more)	VERY LOW
Myocardial infarction (median follow-up 6.5 years)												
1	Cohort	None	None	None	None	None	949 / 19079 (5.0%)	1085 / 19079 (5.7%)	0.87	0.80 – 0.95	7 fewer per 1,000 (from 3 fewer to 11 fewer)	LOW
Congestive heart failure (median follow-up 6.5 years)												
1	Cohort	None	None	None	None	None	2496 / 19079 (13.1%)	2715 / 19079 (14.2%)	0.92	0.87 – 0.97	10 fewer per 1,000 (from 4 fewer to 16 fewer)	LOW
Cerebrovascular accident morbidity (median follow-up 6.5 years)												
1	Cohort	None	None	None	None	None	1057 / 19079 (5.5%)	1251 / 19079 (6.6%)	0.84	0.78 – 0.91	10 fewer per 1,000 (from 6 fewer to 14 fewer)	LOW

1 In one study the population only included patients who had previously undergone brachytherapy (Merrick 2006). 2 Number of events < 100 in one study (Merrick 2006). 3 Wide confidence intervals reported in second study (Efstathiou 2009).

Table 54: GRADE profile: what are the adverse cardiovascular effects of long-term androgen deprivation and how prevalent are they? Sub-group analyses: studies including patients with comorbidities versus studies excluding patients with comorbidities

Quality assessment							Number of events		Relative effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ADT**	**No ADT**	**RR**	**95% CI**	**Absolute effect**	**Quality**
Cardiovascular mortality in patients with no comorbidities (median follow-up 3.8 years)												
1	Cohort	None	None	Serious	Serious [1]	None	51 / 1015 (5.0%)	80 / 3877 (2.1%)	2.44	1.73 – 3.44	28 more per 1,000 (from 15 more to 47 more)	VERY LOW
Cardiovascular mortality in patients with comorbidities (median follow-up 3.8 years)												
6	2 cohorts & 4 RCTs	None	Serious [2]	Serious	Serious [1]	None	402 / 7627 (5.3%)	374 / 11240 (3.3%)	1.24	0.78 – 1.95	8 more per 1,000 (from 7 fewer to 30 more)	VERY LOW
Cerebrovascular accident morbidity in patients with no comorbidities (median follow-up not reported)												
1	Cohort	Serious [3]	None	Serious	Serious [1]	None	11 / 64 (17.2%)	57 / 301 (18.9%)	0.91	0.50 – 1.63	14 fewer per 1,000 (from 85 fewer to 86 more)	VERY LOW
Cerebrovascular accident morbidity in patients with comorbidities (median follow-up 4.0 – 6.5 years)												
3	Cohorts	Serious [3]	None	None	None	None	4339 / 60985 (7.1%)	5131 / 81556 (6.3%)	1.10	0.86 – 1.41	6 more per 1,000 (from 9 fewer to 26 more)	VERY LOW

1 Wide confidence intervals reported. 2 Some studies report lower risk in ADT patients while other report a higher risk. 3 Inadequately short follow-up where reported.

Table 55: GRADE profile: what are the adverse cardiovascular effects of long-term androgen deprivation and how prevalent are they? Sub-group analyses: randomised controlled trials (RCTs) versus observational studies

Quality assessment							Number of events		Relative effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADT	No ADT	RR	95% CI	Absolute effect	Quality
Cardiovascular mortality (median follow-up 3.8 years)												
4	RCTs	None	Serious[1]	None	Serious[2]	None	292 / 5673 (5.1%)	241 / 5008 (4.8%)	1.01	0.76 – 1.34	0 more per 1,000 (from 11 fewer to 15 more)	LOW
3	Cohorts	None	None	Serious[3]	Serious[4]	None	161 / 2969 (5.4%)	213 / 10109 (2.1%)	2.15	1.33 – 3.46	23 more per 1,000 (from 7 more to 48 more)	VERY LOW

1 Two studies report a decreased risk in ADT patients (D'Amico 2007; Efstathiou 2009) and two report an increased risk (McLeod et al.2006; Roach et al. 2008). 2 Number of events < 100 in two studies (D'Amico 2007; Roach et al. 2008). 3 One study only included patients who had previously undergone brachytherapy (Merrick 2006). 4 Number of events < 100 in two studies (Merrick 2006; Tsai 2007)

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. The limited clinical evidence base for this question made it unfeasible to undertake further economic modelling.

Recommendation	No recommendations made
Relative value placed on the outcomes considered	The GDG considered the outcomes of cardiovascular mortality, cardiovascular morbidity, cerebrovascular accident mortality, cerebrovascular accident morbidity and thromboembolic events to be the most important to identifying what adverse cardiovascular effects were caused by long term androgen deprivation therapy in men with prostate cancer, and their prevalence.
Quality of the evidence	The evidence was assessed by GRADE as very low quality for all outcomes, except cardiovascular morbidity which was assessed as low quality as much of the data was from cohort studies.
Trade-off between clinical benefits and harms	The GDG noted from the evidence that adverse cardiovascular effects do occur with the use of long-term androgen deprivation therapy. It was also noted, following subgroup analyses according to type of androgen deprivation therapy, duration of androgen deprivation therapy and existence of co-morbidities, that the evidence indicated there was no significant difference in the occurrence of adverse cardiovascular effects in men receiving long-term androgen deprivation therapy. However, the GDG acknowledged there was considerable uncertainty around this result in addition to a high degree of heterogeneity in the evidence. Given this uncertainty, the GDG were concerned that stating there was no increased risk of adverse cardiovascular effects could be falsely reassuring to patients, especially since the summary of product characteristics for some androgen deprivation therapies cites potential adverse cardiovascular effects as common. Equally, stating that there was an increased risk of adverse cardiovascular effects could cause unnecessary anxiety for patients because it is not clear from the evidence that this is the case. The GDG also debated whether or not to recommend that the uncertainty over the risks of adverse cardiovascular effects be highlighted to men considering long-term androgen deprivation therapy. However, the patient members of the group cautioned that knowing this uncertainty would not be helpful in assisting a man to make this treatment decision. Therefore the GDG agreed not to make any recommendations on this issue.
Other considerations	The GDG also decided not to make a recommendation for further research in this area because the GDG did not consider it a priority for the guideline.

Update 2014

7.4.2 Hot flushes

Hot flushes can be treated with anti-depressants, the α adrenergic agonist clonidine and hormone therapies such as medroxyprogesterone acetate, cyproterone acetate and diethylstilbestrol). Self-management (such as diet and lifestyle changes) may also be effective, as may complementary therapies.

Clinical question: What is the most effective intervention for hot flushes as a result of long term androgen suppression for prostate cancer?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all pre-specified outcomes is summarised in Tables 56 to 66.

Hot flushes

Very low quality evidence showed a complete resolution of hot flushes in 86% (12/14) of men treated with diethylstilbestrol compared with 0% (0/14) of those receiving placebo (RR 25 95% CI 1.62-385.09) (based on an RCT identified by the previous guideline; Atala *et al*. (1992). Low quality evidence from Gerber *et al*. (2000) compared the effect of low dose (0.05mg) and high dose (0.10mg) estradiol patches on hot flushes in 12 men with advanced prostate cancer receiving leuprolide injections. A moderate or major improvement in hot flushes was seen in 25% of the low dose estradiol group compared with 67% of the high dose group (RR in favour of high dose 2.67 95% CI 0.93-7.69).

One RCT (Loprinzi *et al*. 1994a) of low quality examined the effect of 20mg megestrol acetate on hot flushes in 66 men who had undergone surgical or medical androgen suppression. A significant reduction in both frequency and severity of hot flushes was found in favour of megestrol acetate. 79% of men in the megestrol acetate group and 12% of men in the placebo group reported at least 50% reduction in daily frequency of hot flushes (RR 6.50 95% CI 2.55-16.57). A high quality RCT found greater hot flush reduction was reported in a medroxyprogesterone and cyproterone acetate arm than was seen in a venlafaxine arm (Irani *et al*. 2010). Complete regression of hot flush symptoms was reported in 8% of the venlafaxine group, 37% of the cyproterone group, and 25% of the medroxyprogesterone group.

A low quality RCT of cyproterone acetate versus placebo found a mean number of hot flushes per day of around two during the treatment period compared to 10 during the placebo phase (Eaton & McGuire 1983). The authors reported a significant reduction in incidence of hot flushes with cyproterone acetate. However, it is not specified whether this is versus baseline or placebo.

One RCT (Loprinzi *et al*. 1994b) found no significant difference between clonidine and placebo arms in terms of frequency or severity of hot flushes. Clonidine was associated with increased dry mouth and redness under the patch.

Another RCT of venlafaxine showed a 47% reduction in hot flush score (Irani *et al*. 1994b). However, hormonal therapy with medroxyprogesterone and cyproterone had a significantly larger benefit than did venlafaxine. An unpublished study by Vitolins *et al*. (2011) compared four groups of treatment for hot flushes in androgen-deprived men: placebo pill plus casein protein, soy protein plus placebo pill, venlafaxine plus casein protein, or soy plus venlafaxine. All groups showed a reduction in hot flush score over time but there were no significant differences between groups.

One moderate quality placebo-controlled trial found no improvement in hot flushes for high dose isoflavones compared to placebo (Sharma *et al*. 2009). One RCT found no significant changes in the severity, frequency or duration of hot flashes among men receiving placebo or Dong Quai (a Chinese herbal compound) (Al-Bareeq *et al*. 2010). One trial (Frisk *et al*. 2009) of moderate quality compared electrostimulated acupuncture (EA) and traditional acupuncture (TA) in castrated men (via surgery or GnRH analogue). A decrease of hot flush frequency larger than 50% was reported in 57% of the EA group and 47% of the TA group at 12 weeks (RR 1.22 95% CI 0.60-2.48). At 12 months follow-up 18% of the EA group and

Update 2014

46% of the TA group still experienced a decrease in number of hot flushes of 50% or more (RR 0.26 95% CI 0.04-1.70). This study reported a 78% reduction of hot flush scores in the EA group and a 73% reduction in the TA group, without any statistical analysis.

Adverse events

Very low quality evidence showed diethylstilbestrol was associated with gynacomastia and breast tenderness, but the rates of adverse events were not reported (based on an RCT identified by the previous guideline; Atala *et al*. 1992). Low quality evidence from Gerber *et al*. (2000) compared the effect of low dose (0.05mg) and high dose (0.10mg) estradiol patches on hot flushes in 12 men with advanced prostate cancer receiving leuprolide injections. Painless breast swelling was reported by 4/12 men on high dose estradiol and 1/12 men on low dose estradiol (RR 4.00, CI 0.52 to 30.76).

A high quality RCT found higher adverse event rates in a cyproterone group (25%) compared to a medroxyprogesterone group (12%) and a venlafaxine group (20%) (Irani *et al*. 2010).

A low quality RCT of cyproterone acetate versus placebo found five out of 12 men complained of lethargy, severe enough to reduce dosage in one case (Eaton & McGuire 1983).

No adverse events were reported by a moderate quality placebo-controlled trial of isoflavones compared to placebo (Sharma *et al*. 2009) or an RCT comparing Dong Quai to placebo (Al-Bareeq *et al*. 2010). In a study comparing electrostimulated acupuncture (EA) and traditional acupuncture (TA) in castrated men (via surgery or GnRH analogue), three patients reported adverse events (1 distress, 1 fatigue, 1 hematoma).

Cardiovascular events

None of the included studies reported this outcome.

Health-related quality of life

A high quality RCT found health-related quality of life scores to be high in cyproterone, medroxyprogesterone and venlafaxine groups over time (mean 85 out of 100) (Irani *et al*. 2010). Venlafaxine had the highest scores at 4 week and 8 week follow-up. One moderate quality placebo-controlled trial found no improvement in quality of life for high dose isoflavones compared to placebo (Sharma *et al*. 2009).

Update 2014

Table 56: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: diethylstilbestrol versus control after bilateral orchidectomy

Quality assessment							Number of patients		Relative effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Diethylstil-bestrol**	**Control**	**RR**	**95% CI**	**Absolute effect**	**Quality**
Hot flushes: complete resolution (assessed using patient diary card)												
1	RCT	Very serious[1]	None	None	Serious[2]	None	12 / 14 (85.7%)	0 / 14 (0.0%)	25	(1.62 – 385.1)	Not pooled	VERY LOW
Adverse events (assessed by Clinician)												
1	RCT	Very serious[1]	None	None	Serious[2]	None	Gynecomastia & breast tenderness[3]	Not pooled	Not pooled	Not pooled	Not pooled	VERY LOW
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Methods unclear, no details of randomisation method or allocation concealment. Time points not stated. Baseline characteristics not provided. No formal inclusion or exclusion criteria.

2 Low number of events and small sample size. 3No numbers reported.

Table 57: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: high dose versus low dose oestrogen patches after androgen deprivation therapy

Quality assessment							Number of patients		Relative effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High dose oestrogen**	**Low dose oestrogen**	**RR**	**95% CI**	**Absolute effect**	**Quality**
Hot flushes: moderate or major improvement in symptoms (assessed using patient report)												
1	RCT	Serious [1]	None	None	Serious [2]	None	8 / 12 (66.7%)	3 / 12 (25.0%)	2.67	(0.93 – 7.69)	418 more per 1,000 (from 17 fewer to 1,000 more)	LOW
Adverse events: painless breast swelling (assessed using patient report)												
1	RCT	Serious [1]	None	None	Serious [2]	None	4 / 12 (33.3%)	1 / 12 (8.3%)	4.00	(0.52 – 30.76)	250 more per 1,000 (from 40 fewer to 1,000 more)	LOW
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Method of randomisation and baseline characteristics of participants not reported. No control/placebo group. 2 Low number of events, small sample size and wide confidence intervals.

Table 58: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: megastrol acetate versus control after androgen deprivation therapy

Quality assessment							Number of patients		Relative effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Megastrol acetate**	**Control**	**RR**	**95% CI**	**Absolute effect**	**Quality**
Hot flushes: 50% reduction (assessed using patient report)												
1	RCT	Serious [1]	None	None	Serious [2]	None	26 / 33 (78.8%)	4 / 33 (12.1%)	6.50	(2.55 – 16.57)	667 more per 1,000 (from 188 more to 1,000 more)	LOW
Adverse events												
1	RCT	Serious [1]	None	None	Serious [2]	None	0 / 33 (0.0%)	0 / 33 (0.0%)	Not pooled	Not pooled	Not pooled	LOW
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 No reason for drop-outs or withdrawals. Crossover analysis ignored due to significant carryover effects of megastrol acetate. 2 Single study, small sample of men with prostate cancer.

Table 59: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: medroxyprogesterone acetate (MA) versus venlafaxine (VF) versus cyproterone acetate (CA) after androgen deprivation therapy

Quality assessment							Number of patients			Relative effect (RR 95% CI)			Absolute effect	Quality
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MA**	**VF**	**CA**	**MA vs VF**	**VA vs CA**	**CA vs VF**		
Hot flushes: > 50% improvement in daily score (assessed using patient report)														
1	RCT	None	None	None	None	None	90 / 107 (84.1%)	45 / 102 (44.1%)	84 / 100 (84.0%)	RR 1.91 (1.51 – 2.41)	RR 1.00 (0.89 – 1.13)	RR 1.90 (1.50 – 2.41)	Not pooled	HIGH
Adverse events: ≥ 1 event related to study drug (assessed using patient report)														
1	RCT	None	None	None	Serious[1]	None	13 / 107 (12.1%)	20 / 102 (19.6%)	25 / 100 (25.0%)	RR 0.62 (0.33 – 1.18)	RR 0.49 (0.26 – 0.90)	RR 1.27 (0.76 – 2.14)	Not pooled	MODERATE
Cardiovascular events														
0	-	-	-	-	-	-	-	-	-	-			-	-
Health-related quality of life (assessed using EORTC-QLQ)														
1	RCT	None	None	None	None	None	Not pooled	Not pooled	Not pooled	Not pooled				HIGH

1 Low number of events

Table 60: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: cyproterone acetate (CA) versus control after androgen deprivation therapy

Quality assessment							Number of patients		Relative effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CA**	**Control**	**RR**	**95% CI**	**Absolute effect**	**Quality**
Hot flushes (assessed using patient diary)												
1	RCT	Very serious[1]	None	None	None	None	12	12	Not pooled	Not pooled	Not pooled	LOW
Adverse events (assessed using patient diary)												
1	RCT	Very serious[1]	None	None	Serious[2]	None	5 / 12 (41.7%)	0 / 12 (0.0%)	Not pooled	Not pooled	Not pooled	VERY LOW
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 In Eaton et al (1983) methods unclear. Baeline characteristics not provided. Individual patient data only - no comparison from baseline to end of treatment. No clear statement on withdrawals. 2 Low number of events and wide confidence intervals.

Table 61: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: transdermal clonidine versus control after androgen deprivation therapy

Quality assessment							Number of patients		Relative effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Clonidine**	**Control**	**RR**	**95% CI**	**Absolute effect**	**Quality**
Hot flushes (assessed using patient-reported daily questionnaire)												
1	RCT	Serious [1]	None	None	None	None	38	39	Not pooled	Not pooled	Not pooled	MODERATE
							No significant difference (group means not reported)					
Adverse events (assessed using patient-reported questionnaire)												
1	RCT	Serious [1]	None	None	None	None	39	39	Not pooled	Not pooled	Not pooled	MODERATE
							Clonidine associated with dry mouth & redness under patch (rate not reported)					
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Method of randomisation and allocation concealment not stated. 32% excluded from analysis due to missing data or inadequate treatment.

Table 62: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: venlafaxine and soy protein versus control after androgen deprivation therapy

Quality assessment							Number of patients		Relative effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine + soy protein	Control	RR	95% CI	Absolute effect	Quality
Hot flushes												
1	RCT	Serious [1]	None	None	Serious [2]	None	30	30	Not pooled	Not pooled	Not pooled	LOW
							No significant differences at follow-up					
Adverse events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
1	RCT	Serious [1]	None	None	Serious [2]	None	30	30	Not pooled	Not pooled	Not pooled	LOW
							No significant differences at follow-up					

1 Abstract only - unable to assess risk of bias; 2Small sample size

Table 63: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: soy isoflavones versus control after androgen deprivation therapy

Quality assessment							Number of patients		Relative effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Soy isoflavones**	**Control**	**RR**	**95% CI**	**Absolute effect**	**Quality**
Hot flushes (assessed using Blatt-Kupperman scale)												
1	RCT	None	None	None	Serious [1]	None	17	16	Not pooled	Not pooled	Not pooled	MODERATE
							No significant changes in either group					
Adverse events												
1	RCT	None	None	None	Serious [1]	None	None reported	None reported	Not pooled	Not pooled	Not pooled	MODERATE
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life (assessed using SF-36)												
1	RCT	None	None	None	Serious [1]	None	17	16	Not pooled	Not pooled	Not pooled	MODERATE
							No significant changes in either group					

1 Single study, small sample size

Table 64: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: Dong Quai versus control after androgen deprivation therapy

Quality assessment							Number of patients		Relative effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dong Quai	Control	RR	95% CI	Absolute effect	Quality
Hot flushes (assessed using patient report)												
1	RCT	None	None	None	Serious [1]	None	11	11	Not pooled	Not pooled	Not pooled	MODERATE
							No significant changes in either group					
Adverse events												
1	RCT	None	None	None	Serious [1]	None	0 / 11	0 / 11	Not pooled	Not pooled	Not pooled	MODERATE
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Single study, small sample size

Table 65: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: electrostimulated acupuncture versus traditional acupuncture after androgen deprivation therapy

Quality assessment							Number of patients		Relative effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electro-stimulated	Traditional	RR	95% CI	Absolute effect	Quality
Hot flushes: ≥ 50 reduction (follow-up 12 weeks; assessed using patient diary)												
1	RCT	None	None	None	Serious [1]	None	8 / 14 (57.1%)	7 / 15 (46.7%)	1.22	(0.60 – 2.48)	103 more per 1,000 (from 187 fewer to 691 more)	MODERATE
Hot flushes: ≥ 50 reduction (follow-up 12 weeks; assessed using patient diary)												
1	RCT	None	None	None	Serious [1]	None	2 / 11 (18.2%)	6 / 13 (46.2%)	0.26	(0.04 – 1.70)	342 fewer per 1,000 (from 443 fewer to 323 more)	MODERATE
Adverse events												
1	RCT	None	None	None	Serious [1]	None	1 distress, 1 fatigue, 1 hematoma		Not pooled	Not pooled	Not pooled	MODERATE
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Wide confidence intervals. Low number of events

Table 66: GRADE profile: what is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer? Comparison: dietary and lifestyle changes after androgen deprivation therapy

Quality assessment							Number of patients		Relative effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet & lifestyle changes	Control	RR	95% CI	Absolute effect	Quality
Hot flushes												
0	-	-	-	-	-	-	-	-	-	-	-	-
Adverse events												
0	-	-	-	-	-	-	-		-	-	-	-
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. No further economic modelling was undertaken due to the relatively insignificant cost implications.

Recommendation	**Offer medroxyprogesterone[p] (20mg per day), initially for 10 weeks, to manage troublesome hot flushes caused by long-term androgen suppression and evaluate the effect at the end of the treatment period. [new 2014]** **Consider cyproterone acetate or megestrol acetate[q] (20 mg twice a day for 4 weeks) to treat troublesome hot flushes if medroxyprogesterone is not effective or not tolerated. [new 2014]** **Tell men that there is no good-quality evidence for the use of complementary therapies to treat troublesome hot flushes. [new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of hot flushes, adverse events, cardiovascular events and health related quality of life to be the most relevant to this determining the most effective intervention for hot flushes. The outcome of hot flushes was reported by the evidence for all interventions of interest with the exception of diet and lifestyle changes. The outcome of adverse events was reported for three interventions whilst health-related quality of life was reported for two interventions of interest. The outcome of cardiovascular events was not reported for any of the interventions listed in the PICO for this topic. The GDG also considered the additional outcome of duration of treatment because the recommendation on the use of synthetic progestogens as first-line therapy for the management of troublesome hot flushes in CG58 specified a time period for taking this therapy orally. The GDG were confident any evidence on duration of treatment would have been found by the search because the population for this topic included all drug interventions for hot flushes.
Quality of the evidence	This evidence for hot flushes ranged from very low to high quality as assessed by GRADE. For adverse events it ranged from very low to moderate quality and for health-related quality of life the evidence ranged from low to high quality. The GDG noted that some of the included studies had poor methodological quality, small population sizes and limited information on withdrawal/dropout rates.
Trade-off between clinical benefits and harms	There was high quality evidence for the use of medroxyprogesterone to reduce the frequency and severity of hot flushes in men with prostate cancer treated with long term androgen suppression. Although both

p At the time of publication (January 2014), medroxyprogesterone 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 Good practice in prescribing and managing medicines and devices for further information.

q At the time of publication (January 2014), megestrol acetate 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 Good practice in prescribing and managing medicines and devices for further information.

Update 2014

	cyproterone and megestrol acetate were also shown be effective, the data was of low quality for both drugs. In addition the rate of adverse events was higher in men receiving cyproterone compared to medroxyprogesterone. Therefore the GDG decided to recommend the use of medroxyprogesterone as first-line therapy for the management of troublesome hot flushes and consider cyproterone acetate or megestrol acetate for second line management. The GDG decided not to make any recommendations on the use of diethylstilbestrol because even though it showed some level of effectiveness the evidence was drawn from one trial of very low quality. The use of synthetic progestogens for the management of troublesome hot flushes in CG58 recommended they should be given for a period of two weeks. However the GDG agreed there was no evidence to support this length of treatment and it is not considered to be current practice. The evidence presented separately to the GDG on the treatment duration time for these hormone therapies indicated a time of 10 weeks. Therefore the GDG agreed to include this within the recommendation. One study was identified that compared the use of transdermal clondine versus placebo and subsequently assessed the frequency and severity of hot flushes. No significant difference was found between either arm therefore the GDG decided not to make any statement on the use of clondine in this patient population. There was poor quallity evidence of effect of reducing hot flushing frequency with acupuncture (these trials contained no non-acupuncture arm), and no evidence that either soy isoflavones or Dong Quai help reduced hot flushes compared to placebo. Therefore the GDG agreed that men should be advised there is no good quality evidence for the use of complementary therapies in the management of troublesome hot flushes. No evidence was identified investigating the effects of diet or lifestyle on the frequency of hot flushes in men with prostate cancer treated with long term androgen suppression. Therefore the GDG were not able to make any recommendations for these interventions. The GDG agreed that use of additional hormone therapies will lead to a significant reduction in hot flushes with minimal adverse events and improved quality of life. However they did note that the use of progestogens may have an effect on prostate cancer in patients with advanced disease. No other harms or benefits associated with these recommendations were identified by the GDG.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. It was noted that all the drugs recommended are already being used but acknowledged there may be an additional cost incurred by increasing the treatment duration period from two to ten weeks.

Update 2014

7.4.3 Sexual function

Long term androgen suppression is often offered to men with non-localised disease. It functions to keep the disease under control by shrinking it, reducing its symptoms, or delaying its growth. In locally advanced and advanced cancer it can extend over months or years, or indefinitely. A range of methods for administering the treatment are used (injections, implants, tablets) on a regular, intermittent or 'maximal blockage' basis, and all act by stopping testosterone from reaching (prostate cancer cells).

Loss of sex drive (libido – total or reduced) and erectile problems (erectile dysfunction – ED) are very common side effects of long term androgen deprivation and can lead to physical, psychological, emotional and relationship difficulties. Therapeutic interventions are of two types; physical treatments (for example PDE5 inhibitors, prostaglandins, vacuum pumps and prostheses) and psychosexual counselling.

Clinical question: Which are the most effective interventions (singly or in combination) for sexual dysfunction as a result of long term androgen deprivation for prostate cancer?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all pre-specified outcomes is summarised in Tables 67 to 71

Sexual function

A systematic review of the four RCTs reviewed in the previous guideline provided evidence that oral phosphodiesterase type 5 (PDE5) inhibitors are effective in the medium term (up to 4 months) when used to treat erectile dysfunction after EBRT or radical bilateral nerve-sparing or unilateral nerve-sparing retropubic prostatectomy (Miles *et al*. 2007). The combined results of the two parallel group RCTs for improvements in erections found a significant difference (OR 10.09 95% CI 6.20-16.43) in favour of PDE5 inhibitors. Three trials found significant improvements in successful vaginal intercourse in favour of PDE5 inhibitors. Overall, the PDE5 inhibitors led to improved erectile function in about two-thirds of patients. However, in a subgroup of men with more severe dysfunction at baseline (Brock *et al*., 2003), many fewer reported achieving successful sexual intercourse.

One new placebo-controlled crossover trial (Watkins-Bruner *et al*. 2011) in patients treated with radiotherapy (RT) and neoadjuvant and concurrent ADT found that, based on the improvement in erectile function (IIEF score of ≥4 out of a total possible score of 5), 21% responded to Sildenafil but not placebo; and 3% responded to placebo but not Sildenafil (66% did not respond to either placebo or Sildenafil and 10% responded to both). The mean improvement of those on Sildenafil compared to placebo using the IIEF erectile function domain was 4.03 ($p < 0.001$). There was no Sildenafil effect on the Sexual Adjustment Questionnaire (18% placebo only vs. 23% Sildenafil only). In the previous guideline, four RCTs demonstrated the effectiveness of Sildenafil, Tadalafil and Vardenafil for the treatment of erectile dysfunction (ED) after external beam radiotherapy and prostatectomy. All studies excluded men on ADT, except for Brock *et al*. (2003) who excluded men with low serum testosterone levels.

One prospective case-series study (Teloken *et al*. 2007) explored the effects of ADT on response to Sildenafil in patients with erectile dysfunction (ED) following radiotherapy. Mean erectile function domain score and percent of patients who experienced erectile function domain normalization at each time-point were lower in those with versus those without ADT. The percentage of men responding to Sildenafil at 24 months post-radiotherapy was 61% for those without ADT and 47% for those with ADT ($p=0.032$). This could be because tissue androgenisation is required for optimal response to PDE5 inhibitors. The duration of ADT treatment and testosterone recovery was not reported in this study. No trials which directly compared different PDE5 inhibitors were indentified.

No studies assessing the efficacy of prostaglandins on sexual dysfunction in men treated with ADT were found.

From the previous guideline, a review of placebo-controlled trials in patients with ED of mixed aetiology concluded that intraurethral alprostadil (prostaglandin E1) was beneficial in

Update 2014

increasing the proportion of men achieving at least one successful attempt at sexual intercourse (OR 7.22 95% CI 5.68-9.18) (Urciuoli *et al*. 2004). It was not clear what proportion of patients had ED due to prostate cancer. All the trials included in the review pre-selected men who had a good response to alprostadil before randomisation.

No trials were indentified which assessed the efficacy of psychosexual counselling specific to men with sexual dysfunction following ADT. One systematic review was identified which evaluated the effectiveness of psychosocial interventions in improving sexual and/or relationship functioning for men with prostate cancer and their partners (Chisholm *et al*. 2012). Five out of 11 studies which used a measure of sexual functioning reported significant improvement for at least one arm of their intervention. Four out of these five studies had sexual functioning as a major focus of the intervention and used a face-to-face format run by psychologists/training psychologists. Specific intervention strategies that were unique to those interventions that had a positive effect on sexual functioning were the explicit use of sex therapy techniques, including taking a sexual history, teaching sensate focus, and challenging negative thoughts related to sexuality and masculinity. Of the six studies that found no impact of the intervention on sexual functioning, five had sexual functioning as a minor focus and five used supportive/educative strategies. Only two interventions were delivered face-to-face and nurses were more likely to deliver these interventions, with psychologists delivering two programs. Most studies included in the systematic review were of low methodological quality.

No studies were indentified which evaluated the use of vacuum devices for men with ED following ADT. In the systematic review by Miles *et al*. (2007) one trial was reported which evaluated the effectiveness of a vacuum constriction device (VCD) for inducing erection in 109 men with ED following retropubic prostatectomy (Raina *et al*. 2006). In the intervention group, 81% of those using the VCD successfully had sexual intercourse. At 9 months there was a significant difference in overall sexual function in favour of the intervention group (WMD 4.30 95% CI 2.53-6.07). There was no significant difference in erectile function between the two trial arms.

Update 2014

No studies were indentified which evaluated the use of penile prosthesis for men with ED following ADT. A systematic review by Khera & Goldstein (2011) found no systematic reviews or RCTs of penile prostheses in men with erectile dysfunction of any cause and state that prostheses are likely to be beneficial and are usually considered only after less invasive treatments have failed.

Cardiovascular events

In one trial of the PDE5 inhibitor Vardenafil (Brock *et al*. 2003) tachycardia and chest pain were reported in the intervention group. It is unclear if events occurred in the same individuals.

Localised pain/discomfort and localised bruising/swelling

From the previous guideline, a review of placebo-controlled trials in patients with ED of mixed aetiology found that increased penile pain was reported more frequently in the intraurethral alprostadil (prostaglandin E1) group compared to placebo (30% versus 3% respectively; OR 7.39 95% CI 5.40-10.12).

In a study evaluating the effectiveness of a vacuum constriction device (VCD) for inducing erection in 109 men with ED following retropubic prostatectomy, 23% in the intervention group discontinued treatment, mostly because of discomfort (55%) or penile bruising (20%) (Raina *et al*. 2006).

Infection/erosion and health-related quality of life

These outcomes were not reported by any of the included studies.

Update 2014

Table 67: GRADE profile: which are the most effective interventions (singly or in combination) for sexual dysfunction as a result of long-term androgen suppression for prostate cancer? Comparison: PDE5 inhibitors versus placebo

Quality assessment							Number of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsis-tency	Indirect-ness	Imprecis-ion	Other considerations	PDE5 inhibitors	Placebo	Relative risk	95% CI	Absolute	
Improvement in erections (assessed with: Global Assessment Questionnaire (GAQ))												
2	RCTs	None	None	Serious[1]	None	None	171/251 (68.1%)	28/164 (17.1%)	RR 3.86	(2.74 – 5.43)	488 more per 1000 (from 297 more to 756 more)	MODERATE
Erectile function (assessed with: International Index of Erectile Function (IIEF))												
4	RCTs	None	None	Serious[1]	None	None	-	-	Not pooled	Not pooled	Improvement in erectile function rate ranged from 45% to 67%	MODERATE
Improvement in erectile function (assessed with: International Index of Erectile Function – Q1 (IIEF))												
1	RCT	None	None	None	Serious[2]	None	13/61 (21.3%)	2/61 (3.3%)	RR 6.50	(1.53 – 27.59)	180 more per 1000 (from 17 more to 872 more)	MODERATE
Cardiovascular events (tachycardia and chest pain)												
1	RCT	None	None	Serious[1]	Serious[3]	None	6/233	-	-	-	-	LOW
Localised pain/discomfort												
0	-	-	-	-	-	-	-	-	-	-	-	-
Localised bruising/swelling												
0	-	-	-	-	-	-	-	-	-	-	-	-
Infection/erosion												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

Update 2014

1 Participants included men with erectile dysfunction following prostatectomy or radiotherapy. Men treated with hormonal therapy or those with low serum testosterone were excluded. 2 Low number of events. 3 It is unclear if cardiovascular events occurred in the same individuals. Low number of events

1
2
3

Table 68: GRADE profile: which are the most effective interventions (singly or in combination) for sexual dysfunction as a result of long-term androgen suppression for prostate cancer? Comparison: prostaglandins versus placebo

Quality assessment							Number of patients		Relative effect			
No. of studies*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prosta-glandins**	**Placebo**	**OR**	**95% CI**	**Absolute effect**	**Quality**
Sexual function: ≥ 1 successful sexual intercourse attempts												
2 (from 1 review)	RCTs	Very serious[1]	None	Very serious[2]	None	None	345 / 528 (65.3%)	101 / 573 (17.6%)	7.22	(5.68 – 9.18)	431 more per 1,000 (from 372 more to 486 more)	VERY LOW
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Localised pain/discomfort: proportion of men reporting penile pain												
2 (from 1 review)	RCTs	Very serious[1]	None	Very serious[2]	None	None	170 / 567 (30.0%)	18 / 589 (3.1%)	7.39	(5.40 – 10.12)	158 more per 1,000 (from 115 more to 211 more)	VERY LOW
Localised bruising/swelling: minor urethral trauma												
2 (from 1 review)	RCTs	Very serious[1]	None	Very serious[2]	None	None	26 / 567 (4.6%)	6 / 589 (1.0%)	3.79	(1.88 – 7.65)	27 more per 1,000 (from 9 more to 63 more)	VERY LOW
Infection/erosion												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Incomplete reporting of results and methodological weaknesses (uncertainty about randomisation and whether allocation concealment was performed).

Update 2014

1 2 *2 Participants were pre-selected based on their response to alprostadil before randomisation, which biases the effectiveness in favour of the treatment. It is unclear what proportion of patients had erectile dysfunction due to prostate cancer.*

Table 69: GRADE profile: which are the most effective interventions (singly or in combination) for sexual dysfunction as a result of long-term androgen suppression for prostate cancer? Comparison: psychosocial counselling versus control

Quality assessment							Number of patients		Relative effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychosocial counselling	Control	OR	95% CI	Absolute effect	
Sexual function												
11 (from 1 review)	RCTs	Very serious[1]	None	Serious[2]	Serious[3]	None	Not reported	Not reported	Not pooled	Not pooled	Not pooled	VERY LOW
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Localised pain/discomfort												
0	-	-	-	-	-	-	-	-	-	-	-	-
Localised bruising/swelling												
0	-	-	-	-	-	-	-	-	-	-	-	-
Infection/erosion												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

1 Method of randomisation and concealment of allocation not described adequately in most studies. No sample size calculations. High risk of attrition bias, e.g. in Canada et al. (2005) 39% not complete trial. 2 Population not directly relevant to review question, Men on hormonal therapy were excluded in some studies. Most studies included men with a variety of treatments and disease progression. 3 Wide confidence intervals suggest imprecise data. Small sample sizes.

Table 70: GRADE profile: which are the most effective interventions (singly or in combination) for sexual dysfunction as a result of long-term androgen suppression for prostate cancer? Comparison: vacuum devices versus control

Quality assessment							Number of patients		Relative effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vacuum devices	Control	OR	95% CI	Absolute effect	
Sexual function (assessed using overall score on International Index of Erectile Function (IIEF))												
1	RCT	Serious[1]	Serious[2]	Serious[3]	None	None	74*	35*	Not reported	Not reported	MD 4.30 higher (from 2.53 higher to 6.07 higher)	VERY LOW
Erectile function												
1	RCT	Serious[1]	Serious[2]	Serious[3]	None	None	19 / 60 (31.7%)	13 / 35 (37.1%)	0.78	(0.33 – 1.88)	56 fewer per 1,000 (from 208 fewer to 155 more)	VERY LOW
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Localised pain/discomfort (assessed using patient-reported in those who discontinued treatment)												
1	RCT	Serious[1]	Serious[2]	Serious[3]	None	None	8 / 60	Not reported	Not reported	Not reported	Not reported	VERY LOW
Localised bruising/swelling: penile bruising (assessed using patient-reported in those who discontinued treatment)												
1	RCT	Serious[1]	Serious[2]	Serious[3]	None	None	3 / 60	Not reported	Not reported	Not reported	Not reported	VERY LOW
Infection/erosion												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

*1 No adequate reporting of method of randomisation, allocation concealment or recruitment rate. 2 Due to the lack of studies it is not possible to be confident in the degree of consistency for this outcome. 3 The population was not directly relevant to the PICO which limits the directness of the evidence to the review question. * Better function indicated by higher values.*

Table 71: GRADE profile: which are the most effective interventions (singly or in combination) for sexual dysfunction as a result of long-term androgen suppression for prostate cancer? Comparison: prostheses versus control

Quality assessment							Number of patients		Relative effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vacuum devices	Control	OR	95% CI	Absolute effect	
Sexual function												
0	-	-	-	-	-	-	-	-	-	-	-	-
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	-
Localised pain/discomfort												
0	-	-	-	-	-	-	-	-	-	-	-	-
Localised bruising/swelling												
0	-	-	-	-	-	-	-	-	-	-	-	-
Infection/erosion												
0	-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	-

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. No further economic modelling was undertaken due to the relatively insignificant cost implications.

Recommendation	**Before starting androgen deprivation therapy, tell men and, if they wish, their partner, that long-term androgen deprivation will cause an alteration in sexual experience and possible loss of sexual function. [new 2014]** **Warn men and, if they wish, their partner, about the potential loss of ejaculation and fertility associated with long-term androgen deprivation and offer sperm storage. [new 2014]** **Ensure that men have early and ongoing access to specialist erectile dysfunction services. [new 2014]** **Consider referring men who are having long-term androgen deprivation therapy, and their partners, for psychosexual counselling. [new 2014]** **Offer PDE5 inhibitors to men having long-term androgen deprivation therapy who experience loss of erectile function. [new 2014]** **If PDE5 inhibitors fail to restore erectile function or are contraindicated, offer a choice of:** • **intraurethral inserts** • **penile injections** • **penile prostheses** • **vacuum devices.** **[new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of sexual function, cardiovascular events, localised pain/discomfort, localised bruising/swelling, infection/erosion and health related quality of life to be the most relevant to determining the most effective interventions (offered singly or in combination) for sexual dysfunction. The outcome of sexual function was reported for four of the interventions of interest. The outcome of cardiovascular events was reported for only PDE5 inhibitors. The outcome of localised pain/discomfort was reported for two interventions and the outcome of localised bruising/swelling was reported for two interventions. The outcomes of health related quality of life and infection/erosion were not reported in any of the evidence included in this topic. The GDG noted that for the use of PDE5 inhibitors, headaches, moderate flushing and changes in vision were also reported as outcomes in the evidence but had not been listed in the PICO.
Quality of the evidence	Because the initial search of the evidence (which focused on men being treated with long term androgen suppression) only yielded one relevant study the GDG agreed to broaden the search to include all men who had received treatment for prostate cancer. By doing this the GDG

Update 2014

	acknowledged that they would be updating the topic on effective interventions for managing sexual dysfunction as a side effect of treatment. The evidence for sexual function ranged from very low to moderate quality as assessed by GRADE. For cardiovascular events the evidence was low quality. For localised pain/discomfort and localised bruising/swelling the evidence was very low quality. The GDG noted that the evidence was in-direct, because it included all men who had received treatment for prostate cancer, and therefore the quality score had been downgraded in GRADE. No evidence on combination radiotherapy was identified.
Trade-off between clinical benefits and harms	The GDG noted that the results from the one new study included in the evidence review for this topic supported the existing recommendations in CG58 on managing sexual dysfunction with PDE5 inhibitors. Although there was no evidence assessing the efficacy of the other interventions in men treated with long term ADT the GDG agreed to adopt the recommendations from CG58 and extrapolate them to make them specific to men receiving long term androgen suppression. Although the evidence on psychosexual counselling was drawn indirectly from a systematic review of men treated for prostate cancer it did report a significant improvement in sexual functioning following psychosocial interventions. As the GDG were concerned that current access to psychosexual counselling was variable they agreed to include a recommendation for healthcare professions to consider referring men being treated with long term androgen suppression, and their partners for psychosexual counselling. This would also make the provision to all patients and their partner more equitable.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. It was the opinion of the GDG that no additional costs should be associated with the additional recommendation for psychosexual counselling as these services should already be in place.
Other	For the purposes of this topic, 'long term' was defined as receiving androgen suppression for greater than 6 months.

Update 2014

7.4.4 Osteoporosis

Osteoporosis is common in the ageing man and may be present in men about to commence androgen deprivation therapy. Such therapy may result in the development or worsening of osteoporosis. Interventions used to treat osteoporosis resulting from androgen deprivation therapy include calcium plus vitamin D, bisphosphonates, denosumab and exercise.

NICE has published guidance on the assessment of fracture risk from osteoporosis (NICE, 2012), which includes men on androgen deprivation therapy.

Recommendation	**Do not routinely offer bisphosphonates to prevent osteoporosis in men with prostate cancer having androgen deprivation therapy. [2008]**
Qualifying statement	This recommendation is based on a lack of evidence that the incidence of bone fractures is reduced.

Clinical evidence (2008)

There was consistent evidence from randomised trials (Diamond *et al*. 2001; Greenspan *et al*. 2007; Michaelson *et al*. 2007; Ryan 2006; Magno *et al*. 2005; Smith *et al*. 2001; Smith *et al*. 2003), that treatment with bisphosphonates increases the bone mineral density of the lumbar spine in men receiving hormonal therapy for prostate cancer. However, there was no evidence about the effect of bisphosphonates on the rate of symptomatic fractures: the single trial reporting this outcome had insufficient follow-up (Smith *et al*. 2003). There was no significant difference in the rate of severe adverse effects in bisphosphonate and placebo arms in three trials that reported this outcome (Ryan 2006; Greenspan *et al*. 2007; Smith *et al*. 2003).

Cost-effectiveness evidence (2008)

The literature review identified 153 potentially relevant papers, but none were obtained for appraisal as they did not include any economic evaluations. No economic modelling was undertaken as the GDG concluded evidence from one available RCT showed that bisphosphonates did not reduce or delay the development of symptomatic factures.

Clinical question: What is the most effective intervention for osteoporosis as a result of long term androgen deprivation for prostate cancer?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all pre-specified outcomes is summarised in Tables 72 to 74.

Overall survival

One study (Rao *et al*. 2008) provided low quality evidence of no significant improvement in overall survival between patients receiving bisphosphonates compared to those receiving no intervention.

One study (Smith *et al*. 2012) provided moderate quality evidence of no significant improvement in overall survival between patients receiving denosumab, compared to no intervention (though the number of patients surviving was not reported). The study also reported no significant difference in median survival time between the two groups.

Fracture rate

One study (Klotz *et al*. 2013) provided low quality evidence of no significant difference in overall fracture rate between patients treated with alendronate and those receiving no intervention (p=0.43). Another study (Smith *et al*. 2009) provided moderate quality evidence of no significant difference in overall fracture rate between patients treated with denosumab and those receiving no intervention. However, this study did find a significant reduction in the occurrence of more than one fracture at any site in the denosumab group (p=0.006).

One study (Greenspan *et al*. 2007) provided low quality evidence of no significant difference in the rate of fragility fractures between patients receiving a bisphosphonate (alendronate) and those receiving no intervention.

Smith *et al*. (2003) found moderate quality evidence of no significant difference in the number of newly diagnosed or worsening vertebral fractures between patients receiving zoledronic acid or no intervention. One moderate quality study (Smith *et al*. 2009) also found a significant reduction in vertebral fractures in patients receiving denosumab compared to

Update 2014

those receiving no intervention (RR 0.39 95% CI 0.20-0.78). The results suggest that for every 1,000 patients, 23 fewer vertebral fractures occur in those receiving denosumab alongside their ADT.

Osteonecrosis of the jaw

Seven studies, ranging from 12 to 24 months in follow-up, provided low quality evidence of no occurrence of osteonecrosis of the jaw (ONJ) in those receiving bisphosphonates or no intervention.

One study (Smith *et al*. 2012) provided very low quality evidence of an increased risk of ONJ in patients receiving denosumab compared to those receiving no intervention at 30 months (incidence of 2.3% compared to 0.0%). Another study (Smith *et al*. 2009) found no occurrence of ONJ in either the denosumab or no intervention group at 36 months.

Bone mineral density loss

Sixteen studies provided moderate quality evidence of a lower risk of bone mineral density (BMD) loss at the lumbar spine in patients receiving bisphosphonates than those receiving no intervention. There was a mean BMD increase of 4.1% in the bisphosphonates group and a mean decrease of 2.7% in the no intervention group. Seven of the studies contributed data to the meta-analysis which suggests a mean difference of 7.2% change (95% CI 5.7%-8.7%; p<0.0001) between those receiving bisphosphonates and those receiving no intervention. Six of the studies assessed the effect of zoledronic acid and found a significant mean difference of 7.7% (95% CI 6.1%-9.2%) compared to a no intervention group. The seventh study (Greenspan *et al*. 2007) assessed the effect of alendronate and found a significant mean difference of 5.1% (95% CI 3.5%-6.7%) compared to the no intervention group. One high quality study (Smith *et al*. 2009) reported a significant difference in lumbar spine BMD change between patients receiving denosumab and those receiving no intervention. A BMD increase of 5.6% was reported in the denosumab group compared to a decrease of 1.0% in the no intervention group (p<0.001).

Update 2014

Twelve studies provided low quality evidence of a lower risk of BMD loss at the hip in patients receiving bisphosphonates than those receiving no intervention. There was a mean BMD increase of 1.0% in the bisphosphonates group and a mean decrease of 1.6% in the no intervention group. Five of the studies contributed data to the meta-analysis which suggests a mean difference of 3.0% change (95% CI 2.0%-4.1%; p<0.0001) between those receiving bisphosphonates and those receiving no intervention. Four of these studies assessed the effect of zoledronic acid and found a significant mean difference of 3.6% (95% CI 2.9%-4.3%) compared to a no intervention group. The fifth study (Greenspan *et al*. 2007) assessed the effect of alendronate and found a significant mean difference of 1.4% (95% CI 0.4%-2.4%) compared to the no intervention group. One high quality study (Smith *et al*. 2009) also reported a significant difference in total hip BMD change between patients receiving denosumab and those receiving no intervention, but did not report the estimated percentage change.

Ten studies provided low quality evidence of a lower risk of BMD loss at the femoral neck in patients receiving bisphosphonates than those receiving no intervention. There was a mean BMD increase of 1.2% in the bisphosphonates group and a mean decrease of 2.1% in the no intervention group. Five of the studies contributed data to the meta-analysis which suggests a mean difference of 2.9% change (95% CI 2.1%-3.8%; p<0.0001) between those receiving bisphosphonates and those receiving no intervention. Four of the studies assessed the effect of zoledronic acid and found a significant mean difference of 3.3% (95% CI 2.2%-4.4%) compared to a no intervention group. The fifth study (Greenspan *et al*. 2007) assessed the effect of alendronate and found a significant mean difference of 2.3% (95% CI 0.9%-3.7%) compared to the no intervention group.

Three studies provided low quality evidence of a lower risk of BMD loss at the trochanter in patients receiving bisphosphonates than those receiving no intervention. Two of these studies (Smith *et al*. 2003; Michaelson *et al*. 2007) contributed data to the meta-analysis which suggests a mean difference of 4.0% change (95% CI 2.2%-5.8%; p<0.0001) between those receiving the bisphosphonate zoledronic acid and those receiving no intervention.

Health-related quality of life

One study (Galvao *et al*. 2010) provided moderate quality evidence of the impact of an exercise intervention on the health-related quality of life of prostate cancer patients undergoing ADT. The SF-36 was used to assess general quality of life status and found significantly better scores for general health, vitality and physical health in the exercise group. The QLQ C30 was also used to assess cancer specific quality of life and found the exercise group to have significantly better scores for role, cognitive, fatigue, nausea and dyspnea measures.

Skeletal-related events and change in FRAX score

These outcomes were not reported by any of the included studies.

Update 2014

Table 72: GRADE profile: what is the most effective intervention for osteoporosis as a result of long-term androgen suppression for prostate cancer? Comparison: bisphosphonates versus control

Quality assessment							Number of events / mean change in % points		Effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bisphosph-onates	Control	Relative risk	95% CI	Absolute	Quality
Overall survival (trial follow-up 12 months)												
1 (1)	RCT	None	None	None	Very serious[1]	None	2 / 22 (8.3%)	1 / 26 (3.8%)	2.17	(0.21 – 22.39)	45 more per 1,000 (from 30 fewer to 823 more)	LOW
Fracture rate: any location (trial follow-up 12 months)												
1 (1)	RCT	Serious[12]	None	None	Serious[13]	None	1 / 84 (1.2%)	3 / 102 (2.9%)	0.40	(0.04 – 3.82)	18 fewer per 1,000 (from 28 fewer to 83 more)	LOW
Fragility fracture rate (trial follow-up 12 months)												
1 (1)	RCT	None	None	None	Very serious[2]	None	1 / 25 (4.0%)	1 / 26 (3.8%)	1.04	(0.07 – 15.74)	2 more per 1,000 (from 36 fewer to 567 more)	LOW
Vertebral fracture rate (trial follow-up 12 months)												
1 (0)	RCT	None	None	None	Serious[3]	None	-	-	-	-	-	MODERATE
Osteonecrosis of the jaw (trial follow-up 12-24 months)												
7 (0)	RCTs	None	None	None	Very serious[4]	None	0 / 371 (0.0%)	0 / 332 (0.0%)	-	-	-	LOW
Bone mineral density: lumbar spine (trial follow-up 6-54 months)												
16 (7)	RCTs	None	None	None	Serious[5]	None	+ 4.1%	- 2.7%	-	-	MD 7.2% higher (from 5.7% higher to 8.7% higher)	MODERATE
Bone mineral density: total hip (trial follow-up 6-12 months)												

Quality assessment							Number of events / mean change in % points		Effect			
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bisphosphonates	Control	Relative risk	95% CI	Absolute	Quality
12 (5)	RCTs	None	None	Serious[6]	Serious[7]	None	+ 1.0%	- 1.6%	-	-	MD 3.0% higher (from 2.0% higher to 4.1% higher)	LOW
Bone mineral density: femoral neck (trial follow-up 6-24 months)												
10 (5)	RCTs	None	None	Serious[8]	Serious[9]	None	+ 1.2%	- 2.1%	-	-	MD 2.9% higher (from 2.1% higher to 3.8% higher)	LOW
Bone mineral density: trochanter (trial follow-up 11-12 months)												
3 (2)	RCTs	None	None	Serious[10]	Serious[11]	None	+ 2.0%	- 2.1%	-	-	MD 4.0% higher (from 2.2% higher to 5.8% higher)	LOW

**Figures in brackets are the number of studies which provided the number of cases and were incorporated into the meta-analysis.*
1Number of events < 50 and number of participants < 100 in only study reporting this outcome (Rao et al. 2008).
2Number of events is < 10 and number of participants is < 100 in only study reporting this outcome (Greenspan et al. 2007).
3Number of events < 100 in only study reporting this outcome (Smith et al. 2003).
4No events occurred across studies. Total number of participants was < 100 in two studies (Michaelson et al. 2007; Kapoor et al. 2011).
5Total number of participants < 100 in seven studies (Morabito et al. 2004; Michaelson et al. 2007; Papaioannou et al. 2007; Ryan et al. 2007; Rao et al. 2008; Taxel et al. 2010; Kapoor et al. 2011).
6Patients received ADT for ≤ 1 year in two studies (Ryan et al. 2006; Taxel et al. 2010). 7Number of participants < 100 in five studies (Morabito et al. 2004; Michaelson et al. 2007; Papaioannou et al. 2007; Taxel et al. 2010; Kapoor et al. 2011).
8Patients received ADT for ≤ 1 year in four studies (Smith et al. 2001; Ryan et al. 2006; Ryan et al. 2007; Taxel et al. 2010). 9Number of participants < 100 in five studies (Smith et al. 2001; Michaelson et al. 2007; Ryan et al. 2007; Taxel et al. 2010; Kapoor et al. 2011).
10Patients received ADT for < 1 year in one study (Smith et al. 2001).
11Number of participants < 100 in two studies (Smith et al. 2001; Michaelson et al. 2007).
12Study closed early due to low accrual; only 191 of estimated 216 required sample size recruited (Klotz 2012).
13Number of events < 10 in only study (Klotz 2013).

Table 73: GRADE profile: what is the most effective intervention for osteoporosis as a result of long-term androgen suppression for prostate cancer? Comparison: denosumab versus control

Quality assessment							Number of events / mean change in % points		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Denosumab	Control	RR / HR	(95% CI)	Absolute	
Overall survival (trial follow-up 12-30 months)												
1 (1)	RCTs	None	None	None	Serious[1]	None	-	-	1.01	(0.85 – 1.20)	-	MODERATE
Fracture rate (any location) (trial follow-up 36 months)												
1 (1)	RCT	None	None	None	Serious[2]	None	38 / 734 (5.2%)	53 / 734 (7.2%)	0.72	(0.48 – 1.07)	20 fewer per 1,000 (from 38 fewer to 5 more)	MODERATE
Fracture rate (vertebral) (trial follow-up 36 months)												
1 (1)	RCT	None	None	None	Serious[2]	None	11 / 734 (1.5%)	28 / 734 (3.8%)	0.39	(0.20 – 0.78)	23 fewer per 1,000 (from 8 fewer to 31 fewer)	MODERATE
Osteonecrosis of the jaw (trial follow-up 30-36 months)												
2 (1)	RCTs	None	Serious[3]	None	Very serious[4]	None	33 / 1452 (2.3%)	0 / 1451 (0.0%)	70.13	(4.29 – 1146.76)	-	VERY LOW
Bone mineral density: lumbar spine (trial follow-up 24 months)												
1 (0)	RCT	None	None	None	None	None	+ 5.6%	- 1.0%	-	-	-	HIGH
Bone mineral density: total hip (trial follow-up 24 months)												
1 (0)	RCT	None	None	None	None	None	-	-	-	-	-	HIGH

**Figures in brackets are the number of studies which provided the number of cases and were incorporated into the meta-analysis.*
1Wide confidence intervals reported. 2Data only available for one study; total number of events in study is < 100; wide confidence intervals reported (Smith et al. 2009).
3Large variation in study results. 4Data only available for one study; total number of events in study is < 100 and 0 in one group; wide confidence intervals reported (Smith et al. 2012).

Table 74: GRADE profile: what is the most effective intervention for osteoporosis as a result of long-term androgen suppression for prostate cancer? Comparison: exercise versus control

Quality assessment							Number of events		Effect			Quality
No. of studies*	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	Control	Relative risk	95% CI	Absolute	
Health-related quality of life (trial follow-up 12 weeks)												
1 (0)	RCT	None	None	None	Serious[1]	None	-	-	-	-	-	MODERATE

**Figures in brackets are the number of studies which provided the number of cases and were incorporated into the meta-analysis.*
1Total number of participants in study is < 100.

Cost-effectiveness evidence (see also full evidence review) (2014)

A literature review of published economic evidence identified one relevant paper by Ito 2010. The paper was a cost-effectiveness analysis, which quantified health effects in terms of quality adjusted life years (QALYs) and thus can be considered a cost-utility analysis. The primary results of the analysis by Ito 2010 are summarised in Table 75.

No further health economic analysis was undertaken for this topic because other topics were deemed to be of greater economic importance and were thus given greater priority.

Study quality and results

The study was deemed only partially applicable to the guideline. This was mostly a result of the study considering a country other than the UK (analysis considered a U.S. setting). Minor limitations were identified with the study, with some minor concerns around the use of author assumptions and estimates. However, these were only used where no evidence could be sourced. Furthermore, there were no conflicts of interest identified so there is no reason to suspect that these assumptions were not made objectively.

Evidence statements

The base case results from Ito 2010 suggest that that the use of alendronate therapy in prostate cancer patients with osteoprosis improves effectiveness in QALY terms but that this comes at an increased cost. A strategy of selective alendronate therapy using BMD tests is shown to reduce the additional costs by reducing the number of patients that are treated unnecessarily (i.e. reducing 'over-treatment'). In comparison to no alendronate therapy, selective alendronate therapy provided an additional QALY at a cost of $66,800.

Since the study is US based, it is difficult to draw firm conclusions from the analysis when applying it to the UK setting. However, it does show that selective alendronate therapy is more likely to be cost-effective than universal alendronate therapy.

In addition, the QALYs estimated in the study are potentially underestimates since they are based only on hip fractures. Including other fractures would potentially further increase incremental QALYs and thus improve the cost-effectiveness of selective alendronate therapy in comparison to no alendronate therapy.

Update 2014

Table 75: Modified GRADE table showing the included evidence (Ito 2010) comparing methods of managing and treating osteoporosis

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Ito 2010	Men with prostate cancer	No BMD test or alendronate therapy	$75,474	6.5930	Reference case			One- and two-way sensitivity analysis was conducted in which patient age, history of fractures, cost of alendronate and mean BMD were varied. The results showed that a BMD test with selective alendronate therapy remained the most cost-effective option in most scenarios. However, the strategy of universal alendronate therapy is cost-effective in patients with a high risk of hip fractures. Probabilistic sensitivity analysis (PSA) was not conducted.	Partially applicable Minor limitations
		BMD test and selective alendronate therapy	$75,652	6.5957	$178	0.0027	$66,800		
		No BMD test, universal alendronate therapy	$77,153	6.6041	$1,501	0.0084	$178,700		

1

Recommendation	**Consider assessing fracture risk in men with prostate cancer who are having androgen deprivation therapy, in line with Osteoporosis fragility fracture (NICE clinical guideline 146). [new 2014]** **Offer bisphosphonates to men who are having androgen deprivation therapy and have osteoporosis. [new 2014]** **Consider denosumab for men who are having androgen deprivation therapy and have osteoporosis if bisphosphonates are contraindicated or not tolerated. [new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of bone mineral density loss and fracture rate to be the most important to identifying the most effective intervention to treat osteoporosis resulting from long-term androgen deprivation. The outcomes of skeletal related events and change in fracture risk assessment tool (FRAX) score were not reported for any of the interventions of interest. The GDG noted that whilst the evidence did report the outcome of health-related quality of life, it was not possible to determine if the effect on this outcome was a result of the intervention for osteoporosis. As a result the GDG did not consider this outcome when agreeing their recommendations.
Quality of the evidence	The evidence on bone mineral density loss and fracture rate for bisphosphonates ranged from low to moderate quality as assessed by GRADE. The evidence on fracture rate and bone mineral density loss for denosumab was assessed by GRADE as moderate and high quality respectively. No evidence was found comparing calcium or vitamin D to patients not receiving these supplements. The GDG noted that several studies lacked sufficient power to measure overall survival and fracture rate and that the number of participants was low. The GDG relied on the surrogate outcome of bone mineral density loss to correct for the weakness in the fracture rate data.
Trade-off between clinical benefits and harms	It was noted that evidence had shown reduced fracture rates and improved bone mineral density with the use of bisphosphonates in men with osteoporosis resulting from long-term androgen deprivation. There was also evidence of no increase in the risk of osteonecrosis of the jaw. The GDG noted there was high quality, limited evidence to show that denosumab has a positive impact on vertebral fractures. The GDG were also aware, based on their clinical experience that denosumab is the only treatment option available for men who have osteoporosis resulting from androgen deprivation therapy, but who have contraindications to using bisphosphonates. However the GDG were aware that the use of denosumab has potentially significant cost implications. They therefore recommended that this treatment be considered for men who are intolerant to or have contraindications to using bisphosphonates. Due to the lack of evidence on the use of calcium and vitamin D to treat osteoporosis resulting from long term androgen deprivation, the GDG were not able to make any recommendations on these interventions.
Trade-off between net	The GDG noted that published cost effectiveness evidence had concluded

Update 2014

health benefits and resource use	that bone mineral density test followed by selective alendronate therapy had an ICER of $66,800/QALY (sterling equivalent = £48,238/QALY[r]). The GDG were aware that this study was not UK based and that the quality of life data was often based on assumptions by clinical experts, rather than reported directly by patients. However they also noted that the clinical and cost effectiveness evidence came from trials which had given bisphosphonates to all men on androgen deprivation therapy, not just those with osteoporosis. The GDG considered that the clinical benefits and cost-effectiveness of using bisphosphonates in men with osteoporosis may have been underestimated because the study didn't take into account all types of fractures and limited itself to hip fractures. In addition the calculation of reference costing may have been greater than that applicable in the UK. The GDG therefore agreed to recommend the use of bisphosphonates for treating osteoporosis resulting from long term androgen deprivation.
Other	The GDG acknowledged that NICE guidance already existed about providing fracture risk assessment for men on androgen deprivation therapy. However they were concerned that consideration of such risk assessment is not yet embedded in clinical practice and therefore agreed to specifically highlight these recommendations from CG146.

Update 2014

Research recommendation	**What is the clinical and cost effectiveness of standard care with bisphosphonates compared with denosumab to treat osteoporosis caused by long-term androgen deprivation therapy? [2014]**
Why is this important	Men receiving long-term androgen deprivation therapy for prostate cancer have an increased fracture risk. Osteoporosis (NICE clinical guideline 146) recommends that fracture risk be assessed when starting long-term ADT but the effectiveness of interventions such as bisphosphonates and denosumab in men with an increased fracture risk is not known.

7.425 Gynaecomastia

Gynaecomastia is a common, troublesome complication of long-term bicalutamide monotherapy. Randomised trials have studied the use of tamoxifen and of prophylactic radiotherapy to the breast buds. Although tamoxifen was shown to be an effective treatment of bicalutamide induced gynaecomastia, there is a theoretical concern that, as an anti-oestrogen, it could have an adverse effect on prostate cancer control.

Recommendation	**For men starting long-term bicalutamide monotherapy (>6 months), offer prophylactic radiotherapy to both breast buds within the first month of treatment. Choose a single fraction of 8 Gy using orthovoltage or electron beam radiotherapy. [2008]** **If radiotherapy is unsuccessful in preventing gynaecomastia, weekly tamoxifen[s] should be considered. [2008]**
Qualifying statement	These recommendations are based on GDG consensus, informed by several small RCTs.

[r] 2008 US values converted to 2012 UK values using OECD price list from Cost conversion website: CCEMG – EPPI – Centre Cost Converter. Accessed at: http://eppi.ioe.ac.uk/costconversion/default.aspx

s At the time of publication (January 2014), tamoxifen 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 Good practice in prescribing and managing medicines and devices for further information.

Clinical evidence (2008)

Gynaecomastia

A systematic review (Di Lorenzo *et al*. 2005) considered evidence from randomised trials of radiotherapy or tamoxifen for the prevention and treatment of gynaecomastia and breast pain associated with anti-androgens. A narrative review of the evidence supported the effectiveness of both radiotherapy and tamoxifen, although there were theoretical concerns that, as an anti-oestrogen, tamoxifen could reduce the effectiveness of hormonal therapy.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

7.4.6 Fatigue

Androgen deprivation can cause fatigue and loss of muscle mass which can negatively affect quality of life. It has been suggested that exercise (e.g. resistance, aerobic) and counselling, in particular cognitive behavioural therapy, may be effective at reducing fatigue in men on long term androgren deprivation.

Clinical question: What is the most effective intervention for fatigue as a result of long term androgen suppression for prostate cancer?

Clinical evidence (see also full evidence review) (2014)

Evidence statements

The evidence for all pre-specified outcomes is summarised in Tables 76 to 78

Fatigue

One RCT compared interpersonal counselling with health education for men with prostate cancer (42% treated with hormone therapy) (Badger *et al*. 2011). Improvements in fatigue were higher for patients in the health education group than for those in the counselling group, although wide confidence intervals suggest there could be little difference between the two interventions (MD 5.12 95% CI -3.08-13.32).

Another study provided moderate quality evidence where men with prostate cancer were randomised to one of four groups (physical training; information; physical training plus information; or control) (Berglund *et al*. 2007). There was no significant effect of treatment on fatigue (scores for each group were not reported).

Of nine RCTs assessing the effectiveness of exercise, one did not provide details of the intervention (Oneill *et al*. 2012) but found a significant mean difference in fatigue between exercise interventions and the no intervention group of 0.38 (95% CI 0.11-0.66; p≤0.01). Two studies assessed a home-based exercise programme; one undertaken during radiotherapy and one undertaken whilst undergoing ADT. The remaining six studies investigated the effectiveness of supervised exercise during radiotherapy and ADT. The results of the studies were pooled for aerobic and resistance exercise separately; the pooled results for the home-based exercise studies showed a medium-sized, non-significant reduction in fatigue in favour of the exercise group (SMD 0.27 95% CI -0.04-0.57). The results from two studies after supervised aerobic exercise showed a large though non-significant reduction in fatigue in favour of the exercise group (SMD 0.75 95% CI -0.42-1.93). Because statistical heterogeneity was present (p=0.03) a sensitivity analysis was performed in which the

Update 2014

outlying study (Monga *et al*. 2007) was excluded. This reduced the effect size to a small non-significant reduction in fatigue (SMD 0.23 95% CI -0.21-0.68). The pooled results for two studies of resistance exercise showed a small non-significant reduction in fatigue in favour of the exercise group (SMD 0.20 95% CI -0.07-0.47). The pooled results of two studies of combined aerobic and resistance exercise showed a large-sized significant reduction in fatigue in favour of the exercise group (SMD 0.96 95% CI 0.54.38).

Health-related quality of life

One moderate quality study found that health-related quality of life scores were higher in the health education group compared to interpersonal counselling, but this outcome lacked precision due to wide confidence intervals (MD -2.78 95% CI -6.60-12.16) (Badger *et al*. 2011).

The study providing moderate quality evidence on physical training versus information versus physical training plus information versus control, found no significant effect of treatment on quality of life (scores for each group were not reported) (Berglund *et al*. 2007).

One high quality study found a significant mean difference in health-related quality of life between exercise interventions and the no intervention group of 0.20 (95% CI 0.04-0.36; p≤0.01), but did not provide details of the exercise intervention (Oneill *et al*. 2012).

Update 2014

Table 76: GRADE profile: what is the most effective intervention for fatigue as a result of long-term androgen suppression for prostate cancer? Comparison: interpersonal counselling versus health education

Quality assessment							Number of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interpersonal counselling	Health education	Relative risk	95% CI	Absolute	Quality
Fatigue (assessed using Multidimensional Fatigue Inventory (MFI))												
1	RCT	None	None	None	Serious[1]	None	36*	34*	Not reported	Not reported	MD 5.12 higher (from 3.08 lower to 13.32 higher)	MODERATE
Health-related quality of life (assessed using UCLA Prostate Cancer Index)												
1	RCT	None	None	None	Serious[1]	None	36*	34*	Not reported	Not reported	MD 2.78 lower (from 6.60 lower to 12.16 higher)	MODERATE

**Less fatigue indicated by lower values; score range 20-100. 1 Wide confidence intervals suggest imprecise data*

Table 77: GRADE profile: what is the most effective intervention for fatigue as a result of long-term androgen suppression for prostate cancer? Comparison: physical training plus information versus control

Quality assessment							Number of patients		Effect			Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical training & information	Control	Relative risk	95% CI	Absolute	
Fatigue (assessed using EORTC-QLQ Fatigue symptom scale)												
1	RCT	Serious [1]	None	None	None	None	52*	51*	Not reported	Not reported	Not reported	MODERATE
Health-related quality of life (assessed using EORTC-QLQ)												
1	RCT	Serious [1]	None	None	None	None	52*	51*	Not reported	Not reported	Not reported	MODERATE

**Less fatigue indicated by lower values. 1 Poor methodological quality. No allocation concealment or blinding of assessors. Intention-to-treat analysis stated, although this was unclear from results. Unclear how many patients completed questionnaire at 12 months follow-up as numbers in the figure are different from the tables. Under-powered study.*

Table 78: GRADE profile: what is the most effective intervention for fatigue as a result of long-term androgen suppression for prostate cancer? Comparison: exercise versus control

Quality assessment							Number of patients		Effect			Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	Control	Relative risk	95% CI	Absolute	
Fatigue												
8	RCTs	None	None	None	None	None	337*	328*	Not reported	Not reported	SMD 0.38 higher (from 0.11 higher to 0.66 higher)	HIGH
Health-related quality of life												
8	RCTs	None	None	None	None	None	313*	307*	Not reported	Not reported	SMD 0.20 higher (from 0.04 higher to 0.36 higher)	HIGH

**Less fatigue indicated by higher values.*

Cost-effectiveness evidence (2014)

A literature review of published cost-effectiveness analyses did not identify any relevant papers. No further economic modelling was undertaken due to the relatively insignificant cost implications.

Recommendation	**Offer men who are starting or having androgen deprivation therapy supervised resistance and aerobic exercise at least twice a week for 12 weeks to reduce fatigue and improve quality of life. [new 2014]** **Tell men who are starting androgen deprivation therapy that fatigue is a recognised side effect of this therapy and not necessarily a result of prostate cancer. [new 2014]**
Relative value placed on the outcomes considered	The GDG considered the outcomes of fatigue and health related quality of life to be the most relevant to determining the most effective intervention for fatigue. The GDG agreed to consider the additional outcome of intervention duration, as it was seen to be an important issue.
Quality of the evidence	The evidence on both fatigue and health related quality of life ranged from moderate to high quality, as assessed by GRADE. The GDG noted that in the majority of included studies, men were receiving androgen deprivation therapy at the same time as receiving the interventions. In addition, some of the studies which included interpersonal counselling as an intervention had wide confidence intervals associated with the data and the trial which assessed counselling as an intervention included all men with prostate cancer of which only 26% were reported as being on long term androgen deprivation therapy.
Trade-off between clinical benefits and harms	The GDG noted that the evidence showed there was no significant effect of counselling on fatigue or quality of life. However the GDG agreed that some advice should be given to men starting androgen deprivation therapy about the likelihood of experiencing fatigue and that they should be made aware that fatigue is a recognised side effect of testosterone suppression and not necessarily of prostate cancer. There was high quality evidence from a meta-analysis for the use of exercise in order to reduce the effects of fatigue and quality of life for men with prostate cancer starting or on androgen deprivation therapy. The results for home based exercise, supervised aerobic exercise alone and supervised resistance alone showed non-significant improvements in fatigue in favour of the intervention. However the pooled results of two studies of combined aerobic and resistance exercise showed a significant reduction in fatigue in favour of the exercise group. In addition six high quality studies assessed the effects of exercise on health related quality of life and showed that the intervention having the most beneficial effect was combined. Therefore the GDG agreed to recommend combined supervised aerobic and resistance exercise to reduce fatigue and improve quality of life. The GDG noted that the recommendations in CG58 did not include any advice on the frequency or duration of regular resistance exercise to reduce fatigue. However the GDG noted that the invention duration for combined supervised aerobic and resistance exercise was twice weekly for 12 weeks in both trials where these interventions were assessed. Therefore the GDG decided to recommend that men starting or on

Update 2014

	androgen deprivation therapy should be offered supervised resistance and aerobic exercise for a minimum of 2 times per week for 12 weeks in order to reduce fatigue and improve quality of life. The GDG agreed that the use of supervised resistance and aerobic classes will lead to a significant reduction in fatigue with minimal adverse events and improved quality of life. No harms associated with these recommendations were identified by the GDG. Although the strength of evidence on the use of supervised resistance and aerobic exercise for men with prostate cancer on long term androgen suppression was moderate to high, the GDG were not certain whether a 12 week programme was sufficient. Therefore they agreed to include a research recommendation to assess whether combined supervised aerobic resistant exercise needs to be continued beyond 12 weeks in men receiving long term androgen suppression.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG agreed there would be additional costs incurred by recommending supervised resistance and aerobic exercise programmes twice weekly for 12 weeks but were confident that the strength of the evidence for this intervention justified these costs.
Other	As a result of the recommendations made, the GDG felt that some men (particularly those who were disabled) may have difficulty using these services due to their inability to attend exercise classes or because of poor or non-existent provision of facilities. The GDG agreed that service providers and commissioners should be aware of this issue when implementing these recommendations.

Update 2014

Research recommendation	**What is the effectiveness of continuous compared with 12 weeks of supervised aerobic resistance in reducing fatigue in men receiving androgen deprivation therapy? [2014].**
Why is this important	Supervised aerobic resistant exercise given for 12 weeks has been shown to improve quality of life and reduce side effects for men receiving androgen deprivation therapy for prostate cancer. It is not clear whether continuing the exercise program beyond 12 weeks will result in further improvements..

7.5 References

2014

Alibhai SM, Duong-Hua M, Sutradhar R, *et al*. (2009). Impact of androgen deprivation therapy on cardiovascular disease and diabetes. Journal of Clinical Oncology 27(21): 3452-3458.

Al-Bareeq RJ, Ray AA, Nott L, *et al*. (2010). Dong Quai (angelica sinensis) in the treatment of hot flashes for men on androgen deprivation therapy: results of a randomized double-blind placebo controlled trial. Canadian Urological Association Journal 4(1): 49-53.

Atala A, Amin M, Harty JI (1992). Diethylstilbestrol in treatment of postorchiectomy vasomotor symptoms and its relationship with serum follicle-stimulating hormone, luteinizing hormone, and testosterone. Urology 39(2): 108-110.

Badger TA, Segrin C, Figueredo AJ, *et al*. (2011). Psychosocial interventions to improve quality of life in prostate cancer survivors and their intimate or family partners. Quality of life research 20(6): 833-844.

Berglund G, Petersson LM, Eriksson KC, *et al*. (2007). "Between Men": a psychosocial rehabilitation programme for men with prostate cancer. Acta Oncologica 46(1): 83-89.

Brock G, Nehra A, Lipshultz LI, *et al*. (2003). Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic prostatectomy. J Urol 170: 1278-1283.

Canada AL, Neese LE, Sui D, *et al*. (2005). Pilot intervention to enhance sexual rehabilitation for couples after treatment for localized prostate carcinoma. Cancer 104: 2689-2700.

Calais da Silva Junior FM (2011). Phase III study of intermittent MAB vs. continuous MAB. European Urology Supplements Conference(var.pagings): 2.

Calais da Silva FM (2011). Phase III study of intermittent mab vs continuos mab. Journal of Urology Conference(var.pagings): 4.

Calais da Silva F, Bono A, Whelan P, *et al*. (2003). Intermittent androgen deprivation for locally advanced prostate cancer. Preliminary experience from an ongoing randomized controlled study of the South European urooncological group. Oncology 65 (Suppl 1): 24-8.

Calais da Silva FE, Bono AV, Whelan P, *et al*. (2009). Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Uroncological Group. European Urology 55(6): 1269-77.

Chisholm KE, McCabe MP, Wootten AC, *et al*. (2012). Review: Psychosocial Interventions Addressing Sexual or Relationship Functioning in Men with Prostate Cancer. Journal of Sexual Medicine 9(5): 1246-1260.

Chung SD, Chen YK, Wu FJ *et al*. (2012). Hormone therapy for prostate cancer and the risk of stroke: a 5-year follow-up study. BJU International 109(7): 1001-1005.

Crook JM (2011). A phase III randomized trial of intermittent vs. continuous androgen suppression for PSA progression after radical therapy (NCIC CTG pr.7/swogjpr.7/ctsu jpr.7/ UK intercontinental trial cruke/01/ 013). International Journal of Radiation Oncology Biology Physics Conference(var.pagings): 2.

Crook JM (2011). A phase III randomized trial of intermittent versus continuous androgen suppression for PSA progression after radical therapy (NCIC CTG PR.7/SWOG JPR.7/CTSU JPR.7/ UK Intercontinental Trial CRUKE/01/013). Journal of Clinical Oncology Conference(var.pagings): 15

Crook JM, O'Callaghan CJ, Duncan D, *et al*. (2012). Intermittent androgen suppression for rising PSA level after radiotherapy.[Erratum appears in N Engl J Med 367(23): 2262]. New England Journal of Medicine 367(10): 895-903.

D'Amico AV, Denham JW, Crook J, *et al*. (2007). Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. Journal of Clinical Oncology 25(17): 2420-2425.

Di Lorenzo, G., Autorino, R., Perdona, S. & De, P. S. (2005) Management of gynaecomastia in patients with prostate cancer: A systematic review. Lancet Oncology, 6: 972–979.

Diamond, T. H., Winters, J., Smith, A., De, S. P., Kersley, J. H., Lynch, W. J. & Bryant, C. (2001) The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade: a double blind, randomized, placebo-controlled crossover study. Nature reviews.Cancer., 92: 1444–1450.

Update 2014

Duncan GG (2011). QOL/outcomes of an international phase 3 trial of intermittent v continuous hormone therapy for relapsed prostate CA. Radiotherapy and Oncology Conference(var.pagings): S210.

Eaton AC & McGuire N (1983). Cyproterone acetate in treatment of post-orchidectomy hot flushes. Double-blind cross-over trial. Lancet 322(8363): 1336-1337,

Efstathiou JA, Bae K, Shipley WU, *et al*. (2009). Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27(1): 92-99.

Ehdaie B, Atoria CL, Gupta A, *et al*. (2012). Androgen deprivation and thromboembolic events in men with prostate cancer. Cancer 118(13): 3397-3406.

Frisk J, Spetz AC, Hjertberg H, *et al*. (2009). Two modes of acupuncture as a treatment for hot flushes in men with prostate cancer--a prospective multicenter study with long-term follow-up. European Urology 55(1): 156-163.

Galvao DA, Taaffe DR, Spry N, *et al*. (2010). Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 28(2): 340-347.

Gerber GS, Zagaja GP, Ray PS, *et al*. (2000). Transdermal estrogen in the treatment of hot flushes in men with prostate cancer. Urology 55(1): 97-101.

Greenspan SL, Nelson JB, Trump DL, *et al*. (2008). Skeletal health after continuation, withdrawal, or delay of alendronate in men with prostate cancer undergoing androgen-deprivation therapy. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 26(27): 4426-4434.

Greenspan, S. L., Nelson, J. B., Trump, D. L. & Resnick, N. M. (2007) Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial.[summary for patients in Ann Intern Med. 2007 Mar 20;146(6):I72; PMID: 17371883]. Ann Intern.Med, 146: 416–424.

Hering F, Rodrigues PRT, Lipay MA, *et al*. (2000). Metatstatic adenocarcinoma of the prostate: comparison between intermittent and continuous hormonal treatment. Brazilian Journal of Urology 26(3): 276-282.

Hu JC, Williams SB, O'Malley AJ, *et al*. (2012). Androgen-deprivation therapy for nonmetastatic prostate cancer is associated with an increased risk of peripheral arterial disease and venous thromboembolism. European Urology 164: 61(6): 1119-1128.

Hussain M, Tangen CM, Higano C, *et al*. (2006). Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). Journal of Clinical Oncology 24(24): 3984-90

Hussain M, Tangen CM, Berry DL *et al*. (2013). Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 368: 1314-1325.

Irani J, Salomon L, Oba R, *et al*. (2010). Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. The lancet oncology 11(2): 147-154.

Ito, K. "Cost-effectiveness of fracture prevention in men who receive androgen deprivation therapy for localized prostate cancer." Annals of Internal Medicine 152.10 (2010): 621-29.

Update 2014

Jespersen CG, Norgaard M, and Borre M (2013). Androgen-deprivation therapy in treatment of prostate cancer and riskof myocardial infarction and stroke: a nationwide Danish population-based cohort study. European Urology http://dx.doi.org/10.1016/j.eururo.2013.02.002

Kapoor A, Gupta A, Desai N, *et al*. (2011). Effect of zoledronic acid on bone mineral density in men with prostate cancer receiving gonadotropin-releasing hormone analog. Prostate Cancer

Keating NL, O'Malley AJ, Smith MR *et al*. (2010). Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. Journal of the National Cancer Institute 102(1): 39-46.

Khera M and Goldstein I (2011). Erectile dysfunction. Clinical Evidence 6: 1803.

Kim J, Vaid M, Tyldesley S, *et al*. (2011). Population-based study of cardiovascular mortality among patients with prostate cancer treated with radical external beam radiation therapy with and without adjuvant androgen deprivation therapy at the British Columbia Cancer Agency. International Journal of Radiation Oncology, Biology, Physics 80(3): 742-750.

Klotz L, O'Callaghan CJ, Ding K, *et al*. (2011). A phase III randomized trial comparing intermittent versus continuous androgen suppression for patients with PSA progression after radical therapy: NCIC CTG PR.7/SWOG JPR.7/CTSU JPR.7/UK Intercontinental Trial CRUKE/01/013. Journal of Clinical Oncology Conference(var.pagings): 7

Klotz LH, McNeill IY, Kebabdjian M, *et al*. (2013). A phase 3, double-blind, randomised, parallel-group, placebo-controlled study of oral weekly alendronate for the prevention of androgen deprivation bone loss in nonmetastatic prostate cancer: The Cancer and Osteoporosis Research with Alendronate and Leuprolide (CORAL) study. European Urology 63: 927-935.

Loprinzi CL, Michalak JC, Quella SK, *et al*. (1994). Megestrol acetate for the prevention of hot flashes. The New England journal of medicine 331(6): 347-352.

Magno, C., Anastasi, G., Morabito, N., Gaudio, A., Maisano, D., Franchina, F., Gali, A., Frisina, N. & Melloni, D. (2005) Preventing bone loss during androgen deprivation therapy for prostate cancer: early experience with neridronate. European Urology, 47: 575–580.

McLeod DG, Iversen P, See WA, *et al* (2006). Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU International 97(2): 247-254.

Merrick GS, Butler WM, Wallner KE, *et al*. (2006). Androgen-deprivation therapy does not impact cause-specific or overall survival after permanent prostate brachytherapy. International Journal of Radiation Oncology, Biology, Physics 65(3): 669-677.

Michaelson, M. D., Kaufman, D. S., Lee, H., McGovern, F. J., Kantoff, P. W., Fallon, M. A., Finkelstein, J. S. & Smith, M. R. (2007) Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol, 25: 1038–1042.

Miles CL, Candy B, Jones L, *et al*. (2007). Interventions for sexual dysfunction following treatment for cancer. Cochrane database for systematic reviews Issue 4.

Miller K, Steiner U, Lingnau A, *et al*. (2007). Intermittent versus continuous androgen suppression in advanced prostate cancer - A randomised prospective study. Journal of Urology 177(4): 573.

Michaelson MD, Kaufman DS, Lee H, *et al*. (2007). Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. Journal of clinical oncology 25(9): 1038-1042.

Update 2014

Monga U, Garber SL, Thornby J, *et al*. (2007). Exercise prevents fatigue and improves quality of life in prostate cancer patients undergoing radiotherapy. Archives of Physical Medicine and Rehabilitation 88(11): 1416-1422.

Morabito N, Guadio A, Lasco A, *et al*. (2004). Neridronate prevents bone loss in patients receiving androgen deprivation therapy for prostate cancer. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 19(11): 1766-1770.

Mottet N, van Damme J, Loulidi S, *et al*. (2012). Intermittent hormonal therapy in the treatment of metastatic prostate cancer: A randomized trial. BJU International 110(9): 1262-1269.

Mottet N, Goussard M, Loulidi S, *et al*. (2009). Intermittent Versus Continuous Maximal Androgen Blockade in Metastatic (D2) Prostate Cancer Patients. A Randomized Trial. European Urology Supplements 8(4): 131.

Mottet NA, Goussard M, Loulidi S, *et al*. (2009). Intermittent Versus Continuous Maximal Androgen Blockade in Metastatic (D2) Prostate Cancer Patients. A Randomized Trial. Journal of Urology 181(4): 231-2.

National Institute for Health and Clinical Excellence (2012) Osteoporosis: assessing the risk of fragility fracture. Clinical Guidline 146. London: National Institute for Health and Clinical Excellence

Oneill R, Murray L, O'Sullivan J, *et al*. (2012). A randomised controlled trial to evaluate the efficacy of a dietary and physical activity intervention on prostate cancer patients receiving androgen deprivation therapy. Proceedings of the Nutrition Society Conference(var.pagings).

Papaioannou A, Heras P, Hatzopoulos A, *et al*. (2007). Annual ibandronic acid to prevent gonadotropin included bone loss in men with prostate cancer. Ejc Supplements 5(4): 297-297.

Raina R, Agarwal A, Ausmundson S, *et al*. (2006). Early use of vacuum constriction device following radical prostatectomy facilitate early sexual activity and potentially earlier return to erectile function. International Journal of Impotence Research 18: 77-81.

Rao MP, Kumar A, Goyal NK, *et al*. (2008). Prevention of bone mineral loss by zoledronic acid in men with prostate carcinoma receiving androgen deprivation therapy: a prospective randomized trial in an indian population. Current Urology 2(2): 79-86.

Roach M, Bae K, Speight J, *et al*. (2008). Short-term neoadjuvant androgen deprivation therapy and external beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. Journal of Clinical Oncology 26: 585-591.

Ryan, C. W. (2006) Zoledronic acid initiated during the first year of androgen deprivation therapy increases bone mineral density in patients with prostate cancer. The Journal of urology, 176: 972–978.

Ryan CW, Huo D, Bylow K, *et al*. (2007). Suppression of bone density loss and bone turnover in patients with hormone-sensitive prostate cancer and receiving zoledronic acid. BJU International 100(1): 70-75.

Ryan CW, Huo D, Demers LM, *et al*. (2006). Zoledronic acid initiated during the first year of androgen deprivation therapy increases bone mineral density in patients with prostate cancer. The Journal of urology 176(3): 972-978.

Salonen AJ, Viitanen J, Ala-Opas M, *et al*. (2006). Finnish multicenter study to compare intermittent and continuous androgen deprivation in patients with advanced prostate cancer. Journal of Urology 175(4): 386.

Update 2014

Salonen AJ, Viitanen J, Lundstedt S, *et al*. (2008). Finnish multicenter study comparing intermittent to continuous androgen deprivation for advanced prostate cancer: interim analysis of prognostic markers affecting initial response to androgen deprivation. The Journal of urology 180(3): 915-9.

Salonen AJ, Taari K, Ala-Opas M, *et al*. (2012). The finnprostate study VII: Intermittent versus continuous androgen deprivation in patients with advanced prostate cancer. Journal of Urology 187(6): 2074-2081.

Salonen AJ, Taari K, Ala-Opas M, *et al*. (2012). Finnprostate study VII: Intermittent versus continuous androgen deprivation in patients with advanced prostate cancer. European Urology Supplements 11(1): E131-E131.

Salonen AJ, Taari K, Ala-Opas M, *et al*. (2013). Advanced prostate cancer treated with intermittent or continuous androgen deprivation in the randomised finnprostate study VII: Quality of life and adverse effects. European Urology 63(1): 111-120.

Sharma P, Wisniewski A, Braga-Basaria M, *et al*. (2009). Lack of an effect of high dose isoflavones in men with prostate cancer undergoing androgen deprivation therapy. The Journal of urology 182(5): 2265-2272.

Smith MR, Eastham J, Gleason DM *et al*. (2003). Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. The Journal of urology 169(6): 2008-2012.

Smith MR, Egerdie B, Toriz NH, *et al*. (2009). Denosumab in men receiving androgen-deprivation therapy for prostate cancer. The New England journal of medicine 361(8): 745-755.

Smith MR, McGovern FJ, Zietman AL, *et al*. (2001). Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. The NEJM 345(13): 948-955.

Smith MR, Saad F, Coleman R, *et al*. (2012). Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 379(9810): 39-46.

Taxel P, Dowsett R, Richter L, *et al*. (2010). Risedronate prevents early bone loss and increased bone turnover in the first 6 months of luteinizing hormone-releasing hormone-agonist therapy for prostate cancer. BJU International 106(10): 1473-1476.

Teloken PE, Ohebshalom M, Mohideen N *et al*. (2007). Analysis of the impact of androgen deprivation therapy on Sildenafil citrate response following radiation therapy for prostate cancer. The Journal of Urology 178: 2521-2525.

Tsai HK, D'Amico AV, Sadetsky N, *et al*. (2007). Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. Journal of the National Cancer Institute 99(20): 1516-1524.

Urciuoli R, Cantisani TA, CarliniI M, *et al*. (2004). Prostaglandin E1 for treatment of erectile dysfunction [Cochrane review]. The Cochrane Library

Van Hemelrijck M, Garmo H, Holmberg L, *et al*. (2010a). Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. Journal of Clinical Oncology 28(21): 3448-3456.

Van Hemelrijck M, Adolfsson J, Garmo H, *et al*. (2010b). Risk of thromboembolic diseases in men with prostate cancer: results from the population-based PCBaSe Sweden. Lancet Oncology 11(5): 450-458.

Update 2014

Vitolins M. (2011). Phase III randomized, double-blind, placebo-controlled trial of soy protein and venlafaxine for treatment of hot flashes in men with prostate cancer. Journal of Clinical Oncology Conference(var.pagings): 15.

Watkins Brunner D, James JL, Bryan CJ, *et al*. (2011). Randomized, double-blinded, placebo-controlled crossover trial of treating erectile dysfunction with Sildenafil after radiotherapy and short-term androgen deprivation therapy: results of RTOG 0215. The journal of sexual medicine 8(4): 1228-1238.

Update 2014

8 Metastatic prostate cancer

8.1 Introduction

This chapter addresses the clinical needs of men with prostate cancer that has spread beyond the prostate and pelvic lymph nodes. Bone metastases are common and may cause pain and reduced mobility. The majority of men with metastatic prostate cancer will respond well to hormonal therapy which often keeps the disease controlled for several years. Once the disease becomes refractory to hormonal therapy, the control of symptoms and measures that improve quality of life may become as important as treatments that may prolong life.

8.2 Hormonal therapy

Androgen deprivation by either surgical or medical castration can typically control the disease for several years. Bilateral orchidectomy has been an effective treatment for metastatic prostate cancer for over 60 years. The use of luteinising hormone-releasing hormone agonists (LHRHa) has been compared with bilateral orchidectomy in several randomised trials.

Advantages of bilateral orchidectomy include improved convenience for the patient and treatment adherence but with the disadvantage that it is an irreversible procedure. Advantages of LHRHa include the possibility of intermittent use (see below). Their disadvantages include the cost, and problems with compliance and administration.

LHRHa may be given alone (after a short period of anti-androgen therapy to prevent tumour flare) or in combination with an anti-androgen as combined androgen blockade. When bilateral orchidectomy or LHRHa monotherapy fails an anti-androgen may be added as second-line hormonal therapy.

Recommendation	**Offer bilateral orchidectomy to all men with metastatic prostate cancer as an alternative to continuous luteinising hormone-releasing hormone agonist therapy. [2008]**
Qualifying statement	There are randomised studies which show comparable survival benefit and side effects for bilateral orchidectomy. There is good evidence that bilateral orchidectomy is more cost effective, but the GDG recognised the importance of patient preference in this issue.

Clinical evidence (2008)

Evidence came from a systematic review of thirteen randomised trials of hormonal monotherapy in prostate cancer (Seidenfeld *et al*. 2000; Seidenfeld *et al* 2001). Meta-analysis suggested comparable overall survival benefit between orchidectomy and LHRHa's. The evidence about adverse effects was less reliable due to reporting inconsistencies between trials, although adverse event rates appeared similar in orchidectomy and LHRHa treatment groups.

Cost-effectiveness evidence (2008)

The literature review identified 183 potentially relevant economic evaluations. Ten papers were obtained, but only 2 were considered to be full economic evaluations and reviewed in full. One of these papers was published in Japanese, but an English summary was available.

Bayoumi *et al* (2000) conducted the first evaluation in 2000, as part of a US Agency for Health Care Research (AHRQ) research project. The evaluation represents an extremely comprehensive evaluation that compared 6 different treatment strategies for the first-line

choice of hormone treatment for advanced prostate cancer: 1) diethylstilbestrol [DES] 2) bilateral orchiedctomy 3) non steroidal antiandrogen [NSAA] 4) LHRH monotherapy 5) NSAA in combination with a LHRH and 6) NSAA and bilateral orchidectomy. The economic evaluation was underpinned by a systematic review of appropriate randomised controlled trials (RCTs) and a meta-analysis. A Markov model was also constructed, which took into account the progression of the patients underlying prostate cancer and the side effects due to individual treatments. The framework used for the analysis was a cost-utility analysis from a health services perspective. A cost-effectiveness analysis, using survival as the outcome measure, was also conducted.

The results showed that it cost an extra £6100 and £7500 per additional life-year and QALY gained, respectively, if orchidectomy was used instead of DES. All other treatment options, including LHRH monotherapy, were dominated by orchidectomy (i.e. they were more costly and less effective). These results were robust to most alternative assumptions, except when different utility values were assumed. This finding is important, as the analysis did not take into account patients' preferences for different courses of action, for example, surgical or medical castration. Nonetheless, the authors concluded that orchidectomy was the most cost-effective treatment option.

The second evaluation, by Fujikawa *et al*. (2003) was published in Japanese, but an English summary was available for review. The evaluation was similar to Bayoumi *et al*. in so much that it was based on a review of the literature, meta-analysis and Markov modelling exercise. It also compared a number of different options as first-line hormonal therapies for advanced prostate cancer: 1) DES 2) orchidectomy 3) orchidectomy and NSAA 4) LHRH monotherapy and 5) LHRH monotherapy and NSAA. However, an important difference between the two evaluations is that Fujikawa *et al* (2003) attempted to allow for individual preferences (for medical versus surgical castration) by multiplying the health state utilities of orchidectomy by 0.94 – although a justification for this value is not provided. Thus health outcomes associated with orchidectomy were considered to be of 'less value' compared to purely medical alternatives. The overall quality of the evaluation was judged to be good.

The baseline results from the analysis showed that compared to orchidectomy, LHRH monotherapy cost approximately £17 500 per additional QALY gained. However, it is unclear what the incremental cost-effectiveness ratio would have been if the 0.94 weighting had been removed. It is also unclear whether future health benefits were discounted (in Bayoumi *et al* (2000) they were discounted at 3% per annum). Indeed, minimal sensitivity analysis means that it is difficult to assess the robustness of the results to alternative assumptions.

8.3 Androgen deprivation versus combined androgen blockade (CAB)

Androgen deprivation alone is the standard hormonal therapy for metastatic prostate cancer. It has been postulated that the addition of an oral anti-androgen to androgen deprivation therapy could improve treatment efficacy and a large number of randomised controlled trials have studied the effect on survival.

Recommendation	**Do not offer combined androgen blockade as a first-line treatment for men with metastatic prostate cancer. [2008]**
Qualifying statement	Evidence shows only a modest survival benefit for combined androgen blockade and high costs.

Clinical evidence (2008)

Evidence from 27 randomised trials, summarised in two systematic reviews (Prostate Cancer Trialists 2000; Seidenfeld *et al*. 2001), shows a small survival advantage with combined

androgen blockade using non-steroidal anti-androgens. The estimate of five year overall survival from meta-analysis was 28% for men treated with combined androgen blockade compared with 25% for those treated with androgen deprivation alone (Prostate Cancer Trialists 2000). Using the rate of treatment deprivation as a index of treatment toxicity, Samson, Seidenfeld and co-workers (Samson *et al*. 2002; Seidenfeld *et al*. 2001) reported that men treated with LHRHa alone withdrew from therapy at a rate of 4% or less compared with a rate of 8% or more in men receiving CAB.

8.4 Anti-androgen monotherapy

Anti-androgen monotherapy has been studied in the hope that it would be less toxic than androgen deprivation but with comparable effectiveness. Several randomised trials have shown that loss of sexual function is less marked with anti-androgen monotherapy than with androgen deprivation. There is also evidence that anti-androgen monotherapy causes less reduction in bone mineral density (BMD) than androgen depivation but the significance of changes in BMD in men is not clear. However anti-androgen monotherapy is associated with increased gynaecomastia and is a less effective treatment for metastatic disease than androgen deprivation in terms of overall survival. Anti-androgen monotherapy (bicalutamide 150 mg) is therefore licensed for use in locally advanced disease and not for metastatic disease.

Recommendation	**For men with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia in the hope of retaining sexual function, offer anti-androgen monotherapy with bicalutamide[t] (150 mg). [2008]**
Qualifying statement	Evidence from randomised trials confirms the relative protection from loss of sexual function.
Recommendation	**Begin androgen deprivation therapy and stop bicalutamide treatment in men with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function. [2008]**
Qualifying statement	This recommendation is based on GDG consensus alone.

Clinical evidence (2008)

Meta-analysis of thirteen randomised trials of hormonal monotherapy (Seidenfeld *et al*. 2000; Seidenfeld *et al*. 2001) showed a trend towards poorer overall survival with anti-androgen monotherapy than with castration. The two therapies had different toxicity profiles. Gynaecomastia was more likely with non-steroidal anti-androgens, whereas hot flushes and reduced sexual function were more likely with androgen deprivation. The proportion withdrawing from anti-androgen monotherapy and LHRHa treatment was similar, however, suggesting comparable tolerability (Seidenfeld *et al*. 2000; Seidenfeld *et al*. 2001).

8.5 Hormone-relapsed prostate cancer

There is no universally accepted definition of hormone-relapsed disease. The disease can be considered to be hormone relapsed when androgen deprivation therapy or combined androgen blockade are no longer controlling the prostate specific antigen (PSA) or the symptoms of the disease, or when there is radiological evidence of progression. However hormone-relapsed disease, so defined, may still respond to agents such as abiraterone,

t At the time of publication (January 2014), bicalutamide 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 Good practice in prescribing and managing medicines and devices for further information

oestrogens or corticosteroids that probably work via the androgen pathway. Even when the disease becomes hormone relapsed the androgen receptor on the cancer cells can remain active and LHRHa therapy is usually continued.

There is no known curative therapy for hormone-relapsed disease and so the goals of treatment are to improve survival and quality of life and to control symptoms.

Recommendation	**When men with prostate cancer develop biochemical evidence of hormone-relapsed disease, their treatment options should be discussed by the urological cancer MDT with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate. [2008]**
Qualifying statement	There was GDG consensus that the management of these men is not usually discussed at MDT meetings despite the recommendations in the cancer service guidance 'Improving outcomes in urological cancers' (NICE 2002).

8.6 Chemotherapy

Chemotherapy is usually given to men with symptomatic progression but asymptomatic men with metastatic disease and a rapidly rising PSA may also benefit from chemotherapy.

The combination of docetaxel and prednisolone is the only first-line chemotherapy regime licensed for use in hormone-relapsed prostate cancer. The side effects of this combination can be substantial and it may not be possible to use docetaxel if the disease has progressed to a stage where it is causing significant symptoms. Several trials are investigating the use of docetaxel earlier in the course of the disease.

Signalling through the androgen receptor remains critically important in hormone relapsed prostate cancer and several new drugs have been designed to disrupt this pathway. Recommendations on 'Prostate cancer (metastatic, castration resistant) - abiraterone (following cytoxic therapy)' can be found in NICE technology appraisal guidance 259.

Update 2014

New chemotherapy regimens, targeted therapies and cancer vaccines are currently in clinical trial in prostate cancer.

Recommendations	**Recommendations from NICE TA101:** **Docetaxel is recommended, within its licensed indications, as a treatment option for men with hormone-refractory prostate cancer only if their Karnofsky performance-status score is 60% or more. [2008]** **It is recommended that treatment with docetaxel should be stopped:** • **at the completion of planned treatment of up to 10 cycles, or** • **if severe adverse events occur, or** • **in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies. [2008]** **Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy. [2008]**
Qualifying statement	These recommendations are from 'Docetaxel for the treatment of hormone-refractory metastatic prostate cancer', NICE technology appraisal guidance 101 (2006). They were formulated by the technology appraisal and not by the guideline developers. They have been

	incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support these recommendations can be found at www.nice.org.uk/TA101.

8.7 Oestrogens and steroids

Diethylstilboestrol is a synthetic oestrogen that can reduce the PSA level in men with hormone-relapsed disease. There is also research interest in the use of transdermal oestrogens as an alternative to LHRHa's in newly diagnosed prostate cancer.

Corticosteroids can be very useful in men with hormone-relapsed prostate cancer. Low dose steroids can reduce the production of adrenal androgens in men on androgen deprivation by suppressing adrenocorticotropic hormone (ACTH) secretion from the pituitary. This effect can be achieved by physiological doses of corticosteroids such as dexamethasone, prednisolone or hydrocortisone. Other mechanisms of action have also been postulated to explain the fall in PSA that has been reported with corticosteroids. Higher dose steroids can have an anti-inflammatory effect on bone metastases.

Recommendation	**Offer a corticosteroid such as dexamethasone (0.5 mg daily) as third-line hormonal therapy after androgen deprivation therapy and anti-androgen therapy to men with hormone-relapsed prostate cancer. [2008]**
Qualifying statement	There is evidence from several case series to support this recommendation.

Clinical evidence (2008)

Evidence, from observational studies, suggests a PSA response rate of 50% or more with low dose dexamethasone therapy in men with castration refractory prostate cancer, compared with 21–34% for prednisolone and 21.5% for hydrocortisone.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

8.8 Imaging

The natural history of clinically occult spinal cord compression in prostate cancer is unknown and there is little published data on the use of spinal magnetic resonance imaging (MRI) in this clinical setting. The value of prophylactic irradiation for asymptomatic cord compression is unclear. NICE has published a clinical guideline on metastatic spinal cord compression (NICE, 2008) which may expand these recommendations.

Recommendation	**Offer spinal MRI to men with hormone-relapsed prostate cancer shown to have extensive metastases in the spine (for example, on a bone scan) if they develop any spinal-related symptoms. [2008]**
Qualifying statement	There was strong GDG consensus that it was important to try to identify spinal cord compression in high-risk men as early as possible to enable them to receive the necessary treatment.

Recommendation	**Do not routinely offer spinal MRI to all men with hormone-relapsed prostate cancer and known bone metastases. [2008]**

Recommendation	**Do not routinely offer spinal MRI to all men with hormone-relapsed prostate cancer and known bone metastases. [2008]**
Qualifying statement	There is no evidence to support routine use of MRI in this situation.

Clinical evidence (2008)

Bayley and co-workers (Bayley *et al*. 2001) reported a prospective study using MRI to screen for sub-clinical spinal cord compression in a group of men with vertebral bone metastases from prostate cancer but without symptoms of spinal cord compression. 32% of the group had sub-clinical spinal cord compression on MRI. Another series (Venkitaraman *et al* 2007) reported the results of spinal MRI in men with prostate cancer considered at high risk of developing spinal cord compression, but without functional neurological deficit. Radiological spinal canal compromise was seen in 27% of these men. Neither of the studies reported outcomes following MRI screening for spinal cord compression.

Risk factors for radiological spinal cord compression in men with metastatic prostate cancer were extensive bone metastasis (Bayley *et al*. 2001; Venkitaraman *et al* 2007), duration of hormonal therapy (Bayley *et al*. 2001) and back pain (Venkitaraman *et al*. 2007).

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

8.9 Bone targeted therapies

Men with prostate cancer may benefit from bone targeted therapies such as bisphosphonates, Strontium-89 and Radium-223 (currently not licensed). These may be given as treatment for symptomatic bone metastases or suppress the metastases.

8.9.1 Bisphosphonates

Bisphosphonates are used to treat cancer-related hypercalcaemia and osteoporosis caused by androgen deprivation.

Recommendation	**Do not offer bisphosphonates for the prevention of bone metastases in men with prostate cancer. [2008]**
Qualifying statement	There is inconsistent evidence, from several RCTs, of the effectiveness of bisphosphonates in preventing or reducing complications of bone metastases.
Recommendation	**Bisphosphonates for pain relief may be considered for men with hormone-relapsed prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed. Choose the oral or intravenous route of administration according to convenience, tolerability and cost. [2008]**
Qualifying statement	A systematic review supports this recommendation.

Clinical evidence (2008)

Evidence came from a systematic review of ten randomised trials (Yuen *et al*. 2006). Meta-analysis showed a trend favouring bisphosphonates over placebo for the relief of pain from bone metastases in men with prostate cancer. There was no significant difference, however, between the analgesic consumption of bisphosphonate and placebo groups. Meta-analysis showed a modest reduction in skeletal events with bisphosphonate treatment (using trial authors' definitions of skeletal events). The estimated rates for skeletal events were 37.8%

and 43.0% for the bisphosphonate and placebo groups respectively: an absolute risk difference of 5.2%.

There was inconsistent evidence about the effect of bisphosphonates on the rate of pathological fractures. The rates of spinal cord compression, bone surgery and bone radiotherapy did not differ significantly between bisphosphonate and placebo groups. There were no significant group differences in overall survival or in quality of life.

Cost-effectiveness evidence (2008)

The literature review identified 153 potentially relevant papers, but none were obtained for appraisal as they did not include any economic evaluations. The GDG considered there to be insufficient clinical information available to enable robust economic modelling.

Research recommendation	**Further clinical trials should be conducted to determine if there is a role for bisphosphonates in men with prostate cancer [2008].**
Why is this important	The role of bisphosphonates in preventing or delaying significant complications from bone metastases in prostate cancer is unclear, particularly with the introduction of more effective treatments for men with hormone relapsed prostate cancer. Prospective randomised trials of systemic therapies with or without bisphosphonates are required.

8.9.2 External beam radiotherapy

External beam radiotherapy is an effective way of improving pain from bone metastases and is useful as treatment for spinal cord compression caused by bone metastases in the vertebrae.

8.9.3 Bone-seeking radio-isotopes

Strontium-89 (Sr-89) is a beta-emitting radioactive isotope which is given intravenously and is taken up preferentially in bone metastases. In comparison with standard care, Sr-89 has been shown, in systematic reviews of randomised trials, to improve pain control, and prevent new sites of pain. It has a favourable toxicity profile, but may compromise ability to deliver subsequent myelosuppressive chemotherapy. Samarium-153 has also shown effectiveness in metastatic prostate cancer but has a shorter half-life than Sr-89 and is more complicated to administer. Rhenium-186 is given linked to a bisphosphonate (etidronate) to increase uptake in bone. Radium-223 is an alpha emitter that has been investigated in men with bone metastases from hormone relapsed prostate cancer.

Recommendation	**Strontium-89 should be considered for men with hormone-relapsed prostate cancer and painful bone metastases, especially those men who are unlikely to receive myelosuppressive chemotherapy. [2008]**
Qualifying statement	The evidence of cost effectiveness is weak. However there was GDG consensus that the recommendation should be made based on several RCTs, which demonstrated the clinical benefit of Sr-89.

Clinical evidence (2008)

Systematic reviews of placebo controlled randomised trials (Bauman *et al*. 2005; Brundage *et al*. 1998; Figuls *et al*. 2003; Finlay *et al*. 2005; Loblaw *et al*. 2003; McQuay *et al*. 1999) suggest that strontium-89 (89Sr-chloride) and samarium-153 (153Sm-EDTMP) are effective for the control of pain from bony metastases in men with prostate cancer. There was no evidence of an overall survival benefit for men treated with radioisotopes. Adverse events associated with radioisotope therapy were usually limited to mild myelosuppression. A systematic review of four studies comparing strontium-89 with samarium-153 or rhenium-188

found no significant differences in pain response rate or treatment toxicity (Finlay *et al*. 2005).

Cost-effectiveness evidence (2008)

The literature review on Sr-89 identified 50 potentially relevant papers. Nineteen of these papers were obtained for appraisal of which 2 were identified and reviewed (McEwan *et al* 1994; Malmberg 1997). None contained full economic evaluations, only cost comparisons. All three evaluations compared the costs of providing Sr-89 as an adjunct to radiotherapy to patients with hormone-refractory prostate cancer and bone metastases compared with radiotherapy alone.

The study by McEwan *et al*. (1994) was based on a small Canadian (CAN$) RCT (n=29), although the costing was undertaken retrospectively. All patients were followed-up until death, which was at a median of 30–34 weeks depending on the treatment arm. The study demonstrated a number of clinical benefits including an improvement in quality of life indices. No price year for the costing was provided. The authors stated that the mean treatment cost per patient for the strontium group was Can$16,570 and Can$23,688 for placebo (approximately £7,700–£11,000). However, evidence from within the manuscript suggests that these costs are incorrect, and that the placebo arm was less costly than the strontium-89 arm. No sensitivity analysis was performed, and the evaluation was generally considered to be of poor quality.

The evaluation by Malmberg *et al*. (1997) also evaluated the costs of external radiotherapy alone versus external radiotherapy with Sr-89, from a Swedish societal perspective (that is, both direct healthcare and indirect costs were included). The analysis was based on a single RCT, but longer terms costs were estimated. That is, the time horizon for the analysis was a patient's lifetime. The costs relating to radiotherapy included the costs of skeletal scintigraphy, outpatient visits, inpatients days, and travel to the treatment centre. The costs for Sr-89 included the costs of its administration. Costs were reported in 1993 Swedish prices.

The authors reported that the total additional lifetime cost of Sr-89 treatment were more than offset by cost savings from the postponed external radiotherapy treatments. Reported cost savings were approximately between SEK 3,000–11,000 (approximately £200–£800). However, the main limitation with the analysis was that very few details of the methods were reported. Thus it was difficult to determine the quality of the study. In summary, the overall evidence base to support the use of Sr-89 in this setting was considered to be weak.

8.10 Pelvic targeted therapies

8.10.1 Management of obstructive uropathy

Prostate cancer may result in unilateral or bilateral obstruction of the ureters resulting in impaired renal function.

The development of obstructive uropathy in men with hormone-relapsed prostate cancer is a frequent, potentially fatal, event.

Decompression may allow a return to baseline renal function, palliate symptoms of uraemia and improve quality of life. It may also lead to an earlier discharge from hospital. However it is unlikely to significantly prolong survival, with the average life expectancy of this group of men remaining around 6–12 months.

The most common choices for decompression lie between external placement of a nephrostomy tube under local anaesthetic or the internal insertion of a double J stent from the bladder to the kidney under general anaesthetic. Decompression does have an

associated complication rate and long term morbidity. Medical intervention such as high-dose steroids have also shown promise.

Recommendation	**Offer decompression of the upper urinary tract by percutaneous nephrostomy or by insertion of a double J stent to men with obstructive uropathy secondary to hormone-relapsed prostate cancer. [2008]** **The option of no intervention should also be discussed with men with obstructive uropathy secondary to hormone-relapsed prostate cancer and remains a choice for some. [2008]**
Qualifying statement	These recommendations are based on observational evidence of effectiveness and GDG consensus.

Clinical evidence (2008)

Evidence about urinary tract decompression in men with ureteric obstruction and hormone-refractory prostate cancer came from case series. Most studies concluded that urinary tract decompression, with nephrostomy or ureteral stents, should be considered (Harris & Speakman 2006; Bordinazzo *et al*. 1994; Chiou *et al*.1990; Sandhu *et al*. 1992; Fallon *et al*. 1980). Some, however concluded that, despite any survival benefit, urinary tract decompression was usually not appropriate in this group (Dowling *et al*. 1991; Paul *et al*. 1994). There was insufficient evidence about the relative effectiveness of nephrostomy and ureteral stents: no series directly compared different interventions.

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

8.10.2 Management of haematuria

Locally advanced prostate cancer can result in haematuria caused by bleeding from the prostatic urethra or base of bladder. Endoscopic control of bleeding points can be performed under general anaesthesia. Palliative radiotherapy to the bladder base and prostate also may be effective.

8.10.3 Management of bowel obstruction

Local extension of prostate cancer into the rectum can cause luminal narrowing or complete obstruction. The former can usually be managed by alterations to the diet, the prescription of aperiants and consideration of radiotherapy. Complete obstruction of the lower bowel may require a defunctioning colostomy.

8.11 Palliative care

The understanding of supportive and palliative care on which this guidance is based originates from work by the National Council for Palliative Care. The recommendations in 'Improving supportive and palliative care for adults with cancer' (NICE 2004) apply to men with prostate cancer.

Palliative Care is: "… the active holistic care of patients with advanced, progressive illness. Management of pain and other symptoms and the provision psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality

of life for patients and families." (NICE 2004). Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with other treatments.

8.11.1 Multidisciplinary needs of men with prostate cancer

The present provision of palliative care to National Health Service (NHS) patients involves substantial service provision in the independent and charitable sector as well as service within the NHS.

The management of physical symptoms and the psychological needs of men with metastatic prostate cancer needs to draw on the expertise of many healthcare professionals. The day to day management of men with metastatic prostate cancer is the responsibility of the primary care services but in order to achieve optimum care there needs to be close co-operation between primary care, the urology MDT and generic and specialist palliative care staff.

The long natural history of prostate cancer means that specialist care may start with the urologist, transfer to the oncologist and end with palliative care. Often there will be overlap between services but the man and his carers and professionals need to be clear which service is in overall control at each stage of the illness

The palliative care of these men draws on the expertise of primary care, urological surgeons, orthopaedic surgeons, oncologists, neurosurgeons, neurologists, physicians, support services and experts in pain as well as generic and specialist palliative care providers.

8.11.2 The dying patient

Some men will die from their prostate cancer but many will die from other diseases whilst they have prostate cancer. It is important to identify when men are close to death and ensure that symptom relief and palliative care is available to all. This may require generic or specialist palliative care.

The effective management of symptoms at the end of life, in all care settings, is supported by the use of appropriate care pathways. The Liverpool Care Pathway for the Dying (http://www.sii-mcpcil.org.uk/lcp.aspx) and the Gold Standards Framework (http://www.goldstandardsframework.org.uk/) are models that facilitate the quality of care at the end of life.

Recommendation	**Offer men with metastatic prostate cancer tailored information and access to specialist urology and palliative care teams to address the specific needs of men with metastatic prostate cancer. Offer them the opportunity to discuss any significant changes in their disease status or symptoms as these occur. [2008]** **Offer a regular assessment of needs to men with metastatic prostate cancer. [2008]** **Integrate palliative interventions at any stage into coordinated care, and facilitate any transitions between care settings as smoothly as possible. [2008]** **Discuss personal preferences for palliative care as early as possible with men with metastatic prostate cancer, their partners and carers. Tailor treatment/care plans accordingly and identify the preferred place of care. [2008]** **Ensure that palliative care is available when needed and is not limited to the end of life. It should not be restricted to being associated with hospice care. [2008]**
Qualifying statement	There is evidence from qualitative studies and GDG consensus to support these recommendations.

Clinical evidence (2008)

Literature searches did not find any studies that compared palliative care settings or models in prostate cancer. Several observational studies described experiences with palliative care in particular settings. Although this shows that care is possible in such settings, without comparative studies there was no evidence about which palliative care model or setting was best.

Several themes emerged: the need for multidisciplinary delivery of palliative care (Palmieri & Waxman 2005; Pienta *et al*. 1996; Cunliffe 2003; Ok *et al*. 2005) and the integration of curative and palliative treatment (Ok *et al*. 2005; Pienta *et al*. 1996) during the often long course of the disease (Green *et al*. 2002).

Cost-effectiveness evidence (2008)

The GDG did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

8.12 References

2008

Bauman, G., Charette, M., Reid, R. & Sathya, J. (2005) Radiopharmaceuticals for the palliation of painful bone metastases - A systematic review. Radiotherapy & Oncology, 75: 258.

Bayley, A., Milosevic, M., Blend, R., Logue, J., Gospodarowicz, M., Boxen, I., Warde, P., McLean, M., Catton, C. & Catton, P. (2001) A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate carcinoma. Cancer, 92: 303–310.

Bayoumi, AM *et al*. (2000) Cost-effectiveness of androgen suppression therapies in advanced prostate cancer. Journal of the National Cancer Institute 92(21): 1731–1739

Brundage, M. D., Crook, J. M. & Lukka, H. (1998) Use of strontium-89 in endocrine-refractory prostate cancer metastatic to bone. Provincial Genitourinary Cancer Disease Site Group. Cancer Prevention & Control, 2: 79–87.

Bordinazzo, R., Benecchi, L., Cazzaniga, A., Vercesi, A. & Privitera, O. (1994) Ureteral obstruction associated with prostate cancer: the outcome after ultrasonographic percutaneous nephrostomy. Arch Ital.Urol Androl, 66: 101–106.

Chiou, R. K., Chang, W. Y. & Horan, J. J. (1990) Ureteral obstruction associated with prostate cancer: the outcome after percutaneous nephrostomy. Journal of Urology, 143(5): 957–959

Cunliffe, J. (2003) Reflections on pain management: a case study. Int J Palliative Nursing, -53.

Dowling, R. A., Carrasco, C. H. & Babaian, R. J. (1991) Percutaneous urinary diversion in patients with hormone-refractory prostate cancer.[see comment]. Urology, 37: 89–91.

Eaton, A. C. & McGuire, N. (1983) Cyproterone acetate in treatment of post-orchidectomy hot flushes. Double-blind cross-over trial. Lancet, 2: 1336–1337.

Fallon, B., Olney, L. & Culp, D. A. (1980) Nephrostomy in cancer patients: To do or not to do? Br J Urol, 52: 237–242.

Figuls, M., Martinez, M. J., onso-Coello, P., Català, E., Garcia, J. L. & Ferrandiz, M. (2003) Radioisotopes for metastatic bone pain [Cochrane review]. Cochrane Database of Systematic Reviews.

Finlay, O. G., Mason, M. D. & Shelley, M. (2005) Radioisotopes for the palliation of metastatic bone cancer: a systematic review. Lancet Oncology, 6: 392–400.

Fujikawa, K *et al*. (2003) Cost-utility analysis of androgen ablation therapy in metastatic prostate cancer. Japanese Journal of Urology. 94 (4): 503–512.

Green, J. S., Trainer, A. & Hussain, M. (2002) A study of the comparative use of palliative care services by patients with prostate cancer. J Urol, 167: 69–70.

Harris, M. R. & Speakman, M. J. (2006) Nephrostomies in obstructive uropathy; how should hormone resistant prostate cancer patients be managed and can we predict who will benefit? Prostate Cancer & Prostatic Diseases, 9: 42–44.

Loblaw, D. A., Laperriere, N. J. & MacKillop, W. J. (2003) A population-based study of malignant spinal cord compression in Ontario. Clin Oncol (R Coll.Radiol.), 15: 211–217.

Malmberg, I., *et al*., (1997) Painful bone metastases in hormone-refractory prostate cancer: Economic costs of strontium-89 and/or external radiotherapy. Urology 50(5): 747–753.

McEwan, A.J., *et al*. (1994) A retrospective analysis of the cost effectiveness of treatment with Metastron (89Sr-chloride) in patients with prostate cancer metastatic to bone. Nuclear Medicine Communications 15(7): 499–504.

McQuay, H. J., Collins, S. L., Carroll, D. & Moore, R. A. (1999) Radiotherapy for the palliation of painful bone metastases [Cochrane review]. Cochrane Database of Systematic Reviews.

National Institute for Health and Clinical Excellence (2002) Improving Outcomes in Urological Cancers. NICE cancer service guidance. London: National Institute for Health and Clinical Excellence.

National Institute for Clinical Excellence (2004) Improving Supportive and Palliative Care for Adults with Cancer. NICE cancer service guidance. London: National Institute for Clinical Excellence.

National Institute for Health and Clinical Excellence (2006) Docetaxel for the treatment of hormone-refractory metastatic prostate cancer. NICE technology Appraisal 101. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence (2008) Metastatic spinal cord compression. NICE clinical guideline 75. London: National Institute for Health and Clinical Excellence.

Ok, J. H., Meyers, F. J. & Evans, C. P. (2005) Medical and surgical palliative care of patients with urological malignancies. [Review] [48 refs]. J Urol, 174: 1177–1182.

Palmieri, C. & Waxman, J. (2005) Prostate cancer is best managed by multidisciplinary teams. Pharmacy in Practice, 15: 398–404. Paul, A. B., Love, C. & Chisholm, G. D. (1994) The management of bilateral ureteric obstruction and renal failure in advanced prostate cancer. Br J Urol, 74: 642–645.

Pienta, K. J., Esper, P. S., Naik, H., Parzuchowski, J., Bellefleur, J. & Huber, M. L. (1996) The hospice supportive care program: A new “transitionless” model of palliative care for patients with incurable prostate cancer. J Natl Cancer Inst, 88: 55–56.

Prostate Cancer Trialists (2000) Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet, 355: 1491–1498.

Samson, D. J., Seidenfeld, J., Schmitt, B., Hasselblad, V., Albertsen, P. C., Bennett, C. L., Wilt, T. J. & Aronson, N. (2002) Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer, 95: 361–376.

Sandhu, D. P. S., Mayor, P. E., Sambrook, P. A. & George, N. J. R. (1992) Outcome and prognostic factors in patients with advanced prostate cancer and obstructive uropathy. Br J Urol, 70: 412–416.

Seidenfeld, J., Samson, D. J., Aronson, N., Albertson, P. C., Bayoumi, A. M., Bennett, C., Brown, A., Garber, A., Gere, M., Hasselblad, V., Wilt, T. & Ziegler, K. (2001) Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostate cancer. [Review] [330 refs]. Evidence Report: Technology Assessment (Summary), i-x.

Seidenfeld, J., Samson, D. J., Hasselblad, V., Aronson, N., Albertsen, P. C., Bennett, C. L. & Wilt, T. J. (2000) Single-therapy androgen suppression in men with advanced prostate cancer: A systematic review and meta-analysis. Ann Intern.Med, 132: 566–577.

Venkitaraman, R., Sohaib, S. A., Barbachano, Y., Parker, C. C., Khoo, V., Huddart, R. A., Horwich, A. & Dearnaley, D. P. (2007) Detection of Occult Spinal Cord Compression with Magnetic Resonance Imaging of the Spine. Clin Oncol (R Coll.Radiol.).

Yuen, K. K., Shelley, M., Sze, W. M., Wilt, T. & Mason, M. D. (2006) Bisphosphonates for advanced prostate cancer. [Review] [51 refs]. Cochrane Database of Systematic Reviews, CD006250.

Appendices

Appendix A: Prostate Specific Antigen (PSA)

PSA is a protein, expressed by both normal and malignant prostate cells. Serum PSA levels may rise for reasons such as infection or glandular enlargement due to benign prostatic hyperplasia (BPH) and is therefore not a specific marker for prostate cancer. In addition the levels can fluctuate naturally over time.

The traditional range for normal PSA refers to total PSA levels (tPSA) and anything up to 4 ng/ml was considered satisfactory. Above this value a biopsy would be considered. However, only around 30% of men will have prostate cancer on biopsy with levels between 4 –10 ng/ml (Raaijmakers *et al*. 2004). Conversely as many as 15% of men with PSA values below 4 ng/ml will have cancer, of which some will be clinically significant. As such, a cut-off of 4 ng/ml is not ideal and in clinical practice there is no precise single PSA value in isolation at which to recommend a biopsy.

The concept of age adjusted PSA values evolved to allow for the influence of age on PSA, thus reducing the chance of missing a tumour in a younger man whilst avoiding unnecessary investigation in older men. Thus for a man of 70 years a higher upper PSA limit of 6.5 ng/ml would be acceptable whilst for a man of 45 years a PSA value of 2.5 ng/ml may be considered the upper limit of normal. By lowering the PSA cut off in younger men there is a potential risk that the over detection of clinically insignificant cancers may increase.

Refinements of the traditional PSA test, measuring tPSA have been employed to increase specificity, including the measurement of free/total PSA ratio (f/tPSA) or of complexed PSA (cPSA). These are of most value in the PSA range 2–10 ng/ml and might reduce the number of unnecessary biopsies. In addition, f/tPSA ratio may offer prognostic information - those men with lower ratio potentially harbouring a more aggressive disease.

The concept of ‘PSA kinetics’ is not new but worthy of note. PSA velocity (PSA-V) refers to the absolute rate of PSA change over time. Recent evidence has indicated that PSA-V may need to take into account both age and individual PSA value to optimise interpretation. In clinical practice, a minimum of three values is required over at least 18 months for a meaningful assessment. It may offer prognostic information as to how an individual prostate cancer may behave after diagnosis with a rise in over 2 ng/ml in the year prior to diagnosis predicting a more aggressive disease course or higher post-therapy relapse rate (D’Amico *et al*. 2005). PSA doubling time (PSADT) refers to the time taken for a serum PSA value to double and is also emerging as useful pre-treatment marker of a prostate tumour’s biological potential (Klotz 2005). A calculated PSADT of less than 3 years may indicate a more aggressive tumour course.

A3.1 References

D’Amico AV, Renshaaw AA, Sussman B, Chen MH (2005) Pre-treatment PSA velocity and the risk of death from prostate cancer following external beam radiotherapy. N Eng J Med 294: 440–7

Klotz L (2005) Active surveillance with selective delayed intervention using PSA doubling time for good risk prostate cancer. Eur Urol 47: 16–21

Raaijmakers R, Wildhagen MF Ito K *et al*. (2004) Prostate-specific antigen change in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. Urology 63: 316–20

Appendix B: The cost-effectiveness of multiparametric magnetic resonance imaging (mpMRI) before trans-rectal ultrasound (TRUS) guided prostate biopsy in men with suspected prostate cancer

B.1 Introduction

Men with suspected prostate cancer typically receive a trans-rectal ultrasound (TRUS) guided biopsy of the prostate as the initial diagnosis method. However, while TRUS is excellent at showing the prostate and its zonal anatomy, it cannot highlight small foci of tumour. In particular, TRUS is thought to be particularly poor at detecting anterior, apical and central lesions. Therefore TRUS guided biopsies are somewhat limited with biopsies guided to zones within the gland but generally not to suspicious lesions.

More recently, multiparametric magnetic resonance imaging (mpMRI) techniques have been used in the diagnosis of prostate cancer. These techniques are known to improve the accuracy of biopsies but they are substantially more costly and so may not be cost-effective.

Update 2014

B.1.1 Aims

This economic evaluation aimed to assess the cost-effectiveness of mpMRI before TRUS guided prostate biopsy in men with suspected prostate cancer. The analysis considered the perspective of the National Health Service (NHS).

B.2 Existing Economic Evidence

A systematic literature review was performed to assess the current economic literature in this area. The review identified 827 possibly relevant economic papers relating to prostate cancer Of these, 824 papers were excluded based on the titles and abstracts and thus three full papers relating to the topic at hand were obtained for appraisal. Two of these papers were excluded as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore only one paper, Stadlbauer *et al* 2011, was included in the review of published economic evidence for this topic (see table 80 for further details).

It should be noted that the paper was written in a non-English language (German) and as such would not typically be included in the evidence review. However, given the paucity of other evidence available in this area, an exception was made.

The study estimated the cost-effectiveness of MRI in the diagnosis of prostate cancer prior to the first biopsy and included an analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis. The use of MRI prior to biopsy was found was found to be more effective and more costly than biopsy alone and provided one additional QALY at a cost of €41,331. The authors concluded that it was difficult to make a clear recommendation for or against the use of MRI.

However, the study was deemed to be only partially applicable to our decision problem. This is primarily because the study considered a German health care perspective and, as such, its applicability to the UK health care setting may be limited. Furthermore, potentially serious limitations were identified with the study. Perhaps most notably, a probabilistic sensitivity analysis (PSA) was not conducted.

Update 2014

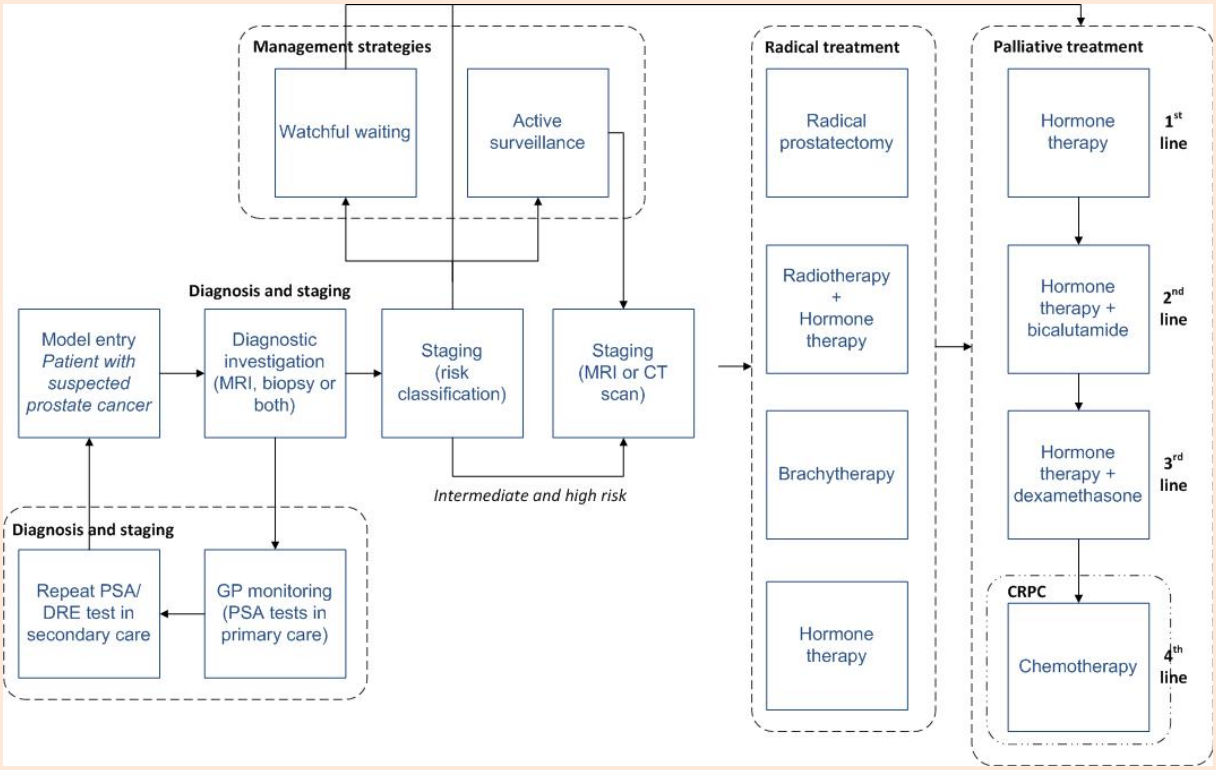
Table 79: Modified GRADE table for Stadlbauer *et al*. 2011

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Stadlbauer *et al*. 2011	Men aged 65 years old with suspected prostate cancer	Biopsy alone	€1,019	13.93 QALYs	Reference			One-way sensitivity analyses were conducted with the estimated ICERs ranging from €12,900 – €48,273 per QALY.	Partially applicable. Not conducted in a UK setting (Germany).	Potentially serious limitations. Probabilistic sensitivity analysis was not conducted.
		MRI followed by biopsy	€1,438	13.94 QALYs	€419	0.01 QALYs	€41,331 per QALY			
Comments: German language study trabslated for evidence review										

B.3 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. This evaluation was based on an existing discrete event simulation (DES) model developed by the London School of Hygiene and Tropical Medicine (LSHTM). The LSHTM designed the model as a way of assessing the feasibility of using full treatment pathway models in guideline development. As such, the model covers the period from referral into secondary care, through the various diagnostic, treatment and management strategies that a patient may receive, to death. As with most economic models, the LSHTM model presents a simplified version of the clinical reality that does not fully encapsulate all the intricacies of managing a complex condition but does capture the key events and outcomes. Figure 56 shows the clinical pathway that was modelled.

Figure 56: Modelled clinical pathway



As the simulation progresses patients have a chance of experiencing one of the relevant competing events at each point in the clinical pathway (assuming that events are both mutually exclusive and exhaustive). Note that unlike most decision model, such as a Markov model, transitions in the model do not occur in fixed time increments i.e. there is no model 'cycle length'. Instead time is calculated separately as a summation of time between events. Thus, the occurrence of competing events is determined using 'time to event' parameters with the competing event with the earliest time being the event which will happen next. These times to event are sampled at the start of the model and are updated as the simulation progresses, reflecting changes in clinical characteristics and age.

As can be seen from the above figure, there are numerous treatment and management strategies that the patient might receive, which are dependent upon the patients clinical stage, risk group (according to D'Amico classification) and the treatment intent (i.e. curative or palliative). Metastatic patients are assumed to receive palliative hormone treatment. Patients with low-risk disease that are suitable for radical treatment are assumed to go to active surveillance with the intention of later receiving radical treatment at the onset of

Update 2014

symptoms or if they choose to do so. Patients with intermediate, high risk and locally advanced disease that are suitable for radical treatment are assumed to transit immediately to radical treatment. Patients who are unsuitable for radical treatment and are not symptomatic are assumed to go to watchful waiting. Symptomatic patients that are unsuitable for radical treatment are assumed to transit immediately to palliative hormone treatment.

Eventually, the patient will experience a death event (either prostate cancer related or through other cause mortality), at which point total life years, quality adjusted life years (QALYs) and costs are calculated for the patient. Thus the model covers the full expected lifetime of each patient. Life years are calculated by adding the total time spent in the model. QALYs are calculated by separating these life years into different 'segments', which reflect the stage of disease and management of the patient. The total time spent in each segment is then multiplied by the associated quality of life (QoL) weighting, which represent the patient's valuation of their health state.

Costs were estimated by adding event related costs to a running total as the model progressed. These costs reflect the various monitoring, management or treatment strategies that the patient may receive including drug costs, treatment costs or any other resource use that may be required (e.g. GP visit). See section on costs for more details.

Costs and benefits were discounted at 3.5% per year as recommended by NICE.

B.4 Disease prevalence and progression

Update 2014

The prevalence of prostate cancer in men being referred for a first biopsy is difficult to estimate and there are no high quality estimations of such a figure. Thus, in the base case, the prevalence of prostate cancer in the population was assumed to be 55% based on the opinion of the guideline development group (GDG). Alternative prevalence rates are explored in sensitivity analysis.

The underlying disease progression rate in the model (i.e. the rate followed by men receiving no treatment) was informed by the watchful waiting arm of a randomised controlled trial of 695 men with localised prostate cancer (Bill Axelson *et al*. 2011). This was chosen as watchful waiting was considered to be the best available proxy for natural progression of disease with no treatment.

This study reported numbers of patients who experienced local progression, metastases and prostate cancer related death at five year and ten year time points. Model calibration techniques were used to derive correlated conditional distributions for these events. A random-walk variant of the Metropolis-Hastings algorithm (Chib *et al*. 1995) based on the methods described by Whyte *et al* 2011 was applied and fitted to the unconditional data from Bill-Axelson *et al* 2011 and other-cause mortality estimates from UK life tables (2007 life tables, Office for National Statistics 2010). The algorithm was run over four separate chains with different starting vectors in order to estimate plausible distributions for each event, conditional on the population having experienced the previous event. A comparison of the maximum a posteriori estimates produced by the calibration techniques against the data reported by Bill Axelson *et al*. 2011 showed that the calibration process provided a good fit to the observed data.

The calibration technique described above allowed the natural history of disease to be modelled as a series of conditional linear transitions from local progression to metastases to prostate cancer related death. This assumes that only metastatic patients can experience prostate cancer related death (i.e. patients with localised prostate cancer must first progress to metastases before they are at risk of prostate cancer related death).

Data on death from causes other than prostate cancer were taken from 2007 national standard mortality rates, and adjusted by removing all deaths attributed to prostate cancer (Office for National Statistics, 2010).

B.5 Clinical effectiveness data

B.5.1 First biopsy

The model was adapted to allow for different diagnostic interventions to be applied to the patients entering with elevated PSA (i.e. patients with and without prostate cancer), with the results of the clinical evidence review used to inform the diagnostic accuracy rates in the model. The results of the evidence review showed that the accuracy improvement associated with adding mpMRI targeted cores to systematic cores is dependent upon the targeting technique that is used. Cognitively targeting TRUS biopsies using a pre-biopsy mpMRI was shown to increase the cancer detection rate by around 2% in comparison to systematic biopsy (Moore *et al*. 2013, Haffner *et al*. 2011, Park *et al*. 2011, Belas *et al*. 2012 and Delongchamps *et al*. 2013). Whereas, TRUS biopsy navigation using mpMRI and ultrasound registration, in comparison to systematic biopsy alone, increased prostate cancer detection by 14% and 20% when using rigid and elastic registration respectively (Delongchamps *et al*. 2013).

Update 2014

Note that since the number of patients included in the study assessing fusion mpMRI strategies (Delongchamps *et al*. 2013) was relatively small, it was decided that the data on rigid and elastic registration should be pooled into one ‘fusion mpMRI’ strategy. When combining the data, the fusion mpMRI strategy was shown to increase prostate cancer detection by 17% in comparison to systematic biopsy alone.

A limitation with the clinical data identified in the evidence review is that it used one of the interventions under consideration as the reference standard (combined mpMRI targeted and systematic biopsy cores). Therefore, the number of false negatives was unknown. To account for this, the sensitivity values reported in the clinical evidence were adjusted using another estimate for the number of false negatives. Some studies have attempted to estimate the proportion of false negatives when performing a TRUS biopsy by investigating the accuracy of ex vivo prostate biopsies. Studies by Fink *et al*. 2001 and Serefoglu *et al*. 2013 both found that a substantial proportion of cancers were missed by a 10-core and 12-core TRUS biopsy, respectively (22% in Fink *et al*. 2001 and 32% in Serefoglu *et al*. 2013).

However the GDG thought that, as these studies were ex vivo, they were likely to underestimate the true number of false negatives. Thus in the base case analysis, it was assumed that systematic TRUS biopsy would have a sensitivity of 45% (implying that 55% are false negatives). This assumption was based on the estimations of the GDG, who expected that there would be a cancer detection rate of around 25% at the first biopsy with a cancer prevalence of 55%[u].

The influence of using the evidence based estimates for false negatives with systematic TRUS biopsy (from Serefoglu *et al*. 2013) was assessed in a sensitivity analysis.

u TRUS sensitivity can thus be back calculated as 0.25/0.55, such that sensitivity (45%) multiplied by prevalence (55%) gives the expected cancer detection rate (25%)

To estimate the improved sensitivity associated with adding cores detected by mpMRI, the relative increases in sensitivity from the evidence review were applied (1.05 and 1.43 for cognitive mpMRI and fusion mpMRI, respectively) to the estimated TRUS sensitivity (45%). Thus, the adjusted sensitivity values for the systematic + cognitive mpMRI biopsy strategy and systematic + fusion mpMRI biopsy strategies were 48% and 65%, respectively.

The accuracy of the diagnostic strategies is thought to be highly dependent upon tumour location. Thus, in the model, the overall sensitivity values reported above were stratified into different 'sensitivity' probabilities for posterior and anterior tumours based on reported accuracy rates from Haffner *et al*. 2011[v]. The evidence from Haffner *et al*. 2011 showed that the strategy using mpMRI had substantially better detection rates in patients with anterior cancer (relative positivity of 1.26) and an equivalent detection rate in patients with posterior cancer. The sensitivity values applied in the model are shown in table 80.

Table 80: Sensitivity values applied in the model

Tumour location	Systematic TRUS biopsy	Systematic + cognitively targeted mpMRI biopsies		Systematic + fusion targeted mpMRI biopsies	
	Sensitivity	Relative rate	Sensitivity	Relative rate	Sensitivity
Overall	45%*	1.05	48%	1.43	65%
Posterior	47%	1.01	48%	1.38	65%
Anterior	38%	1.26	48%	1.73	65%

** Varied using beta distribution in the PSA (alpha = 45, beta = 55)*
All other variables are updated in the PSA using relative rates in comparison the the overall TRUS sensitivity

A further limitation with the evidence base was that false positives were not reported and, as such, specificity values could not be estimated. Therefore, it has been assumed that all three strategies (TRUS, systematic + cognitive mpMRI biopsy and systematic + fusion mpMRI biopsy) have 100% specificity. While this is almost certainly an overestimate, its influence on the cost-effectiveness results should not overstated as it is incremental differences between strategies that drive cost-effectiveness results and there is little reason to suspect significant specificity difference between the strategies. Ultimately, both methods are reliant upon the pathological assessment of cores as the indicator of whether cancer has or has not been detected.

Update 2014

B.5.2 Subsequent management and biopsies

Patients that are found to be positive at the first biopsy will have their disease level staged and will go onto receive the appropriate treatment or management strategy (see later sections for more detail on this). Patients that are not found to be positive at the first biopsy are assumed to remain suspicious and, as such, will most likely have a further biopsy. Following the advice of the GDG, it was assumed that patients that only had a systematic TRUS biopsy as the initial investigation method would have the possibility of having a rebiopsy scheduled three months later (assumed that 50% would receive this in the base case). Whereas, patients that underwent a strategy using mpMRI as the initial investigation method would not be offered a scheduled rebiopsy. This reflects the GDG's view that clinicians would feel more comfortable about the likely absence of disease had a patient undergone a mpMRI and biopsy as the first investigation and, as such, a scheduled rebiopsy would not be required.

Those patients not receiving a scheduled rebiopsy i.e. everyone in mpMRI groups and 50% of patients that received TRUS alone, are assumed to enter into a strategy of PSA monitoring by their GP. Patients will receive a PSA test every six months, with the possibility of having a repeat biopsy if it is felt to be warranted. Owing to a lack of evidence on the proportion of patients that are likely to require subsequent investigation, assumptions were

v Note that Haffner *et al*. 2011 was the only study to provide this level of detail

necessary. Thus, it was assumed that 25%, 50% and 100% of patients would have a subsequent investigation after 1 year, 2 years and 3 years of PSA monitoring, respectively. Thus, essentially, all patients undergoing PSA monitoring will eventually require a subsequent investigation (if they do not experience a fatal event in the interim).

Where patients do undergo a second investigation, it is assumed that 50% are performed with TRUS and the other 50% are performed using mpMRI (under cognitive targeting), with the result of the mpMRI used to decide whether a biopsy is necessary. This assumption reflects current variation in how patients undergoing a second investigation are managed in the NHS. For consistency, the diagnostic accuracy of these techniques was based on the same evidence used in the initial investigation (Haffner *et al*. 2011, Park *et al*. 2011, Belas *et al*. 2012 and Delongchamps *et al*. 2013). However, in this instance, we are interested in the comparison systematic TRUS biopsy and cores cognitively targeted to suspicious areas on the mpMRI scan[w]. The sensitivity and specificity values of the two diagnostic strategies that could be used as the second investigation are shown in table 81.

Table 81: Sensitivity and specificity of second investigation strategies

Tumour location	Systematic TRUS biopsy		Cognitively targeted biopsies		
	Sensitivity	Specificty	Relative rate	Sensitivity	Specificty
Overall	45%*	100%	0.88	40%	60%
Posterior	47%	100%	0.78	37%†	60%
Anterior	38%	100%	1.26	48%‡	60%

** Varied using beta distribution in the PSA (alpha = 45, beta = 55)*
† Varied using beta distribution in the PSA (alpha = 37, beta = 63)
‡ Varied using beta distribution in the PSA (alpha = 48, beta = 52)

Update 2014

Patients found to be negative at the second biopsy stage are assumed to enter PSA monitoring and are subject to the same assumptions described above (following a first negative biopsy). It was assumed that the third biopsy performed would be a saturation biopsy (20-30 biopsy cores) with an assumed sensitivity of 100% i.e. all cancers are detected at this stage.

The assumption of 100% sensitivity at the third biopsy stage combined with the assumption that patients entering PSA monitoring will require a rebiopsy at some point, essentially ensures that all cancers are eventually detected (if the patient does not experience a fatal event between biopsies). This represents a conservative approach that favours less sensitive diagnostic strategies (systematic TRUS biopsies in our analysis). The underlying principle of this approach is that where there is considerable uncertainty that necessitate assumptions, these assumptions should favour the comparator and not the intervention under investigation. The influence of changes to these assumptions is explored in sensitivity analysis.

The model assumes that no further biopsies would be indicated after the third biopsy i.e. a maximum of three biopsies are modelled in the analysis. This assumption implies that patients without prostate cancer would not remain suspicious following a negative saturation biopsy.

B.5.3 Alternative strategy

Note that the results of the clinical evidence review also suggested that a strategy of only biopsying men with positive mpMRI results (i.e. targeted biopsies only) may be beneficial by reducing the number of unnecessary biopsies undertaken. However, the GDG had reservations about the evidence base in this area and were uncomfortable with a targeted biopsy strategy because of the possibility of missing potentially significant cancers. Therefore

w This is in contrast to the first biopsy where we are interested in the comparison of systematic TRUS biopsy and targeted biopsies in addition to systematic TRUS biopsies

this strategy was not incorporated in the base case analysis but is explored further in one of the sensitivity analyses.

B.5.4 Incidence of biopsy-related complications

Patients undergoing biopsies were assumed to be at risk of experiencing biopsy complications, with complications categorised into hospital admissions or biopsy related consultations. The probabilities of these adverse events occurring were sourced from studies by Nam *et al*. 2010 and Rosario *et al* 2012 and are shown in table 82.

Table 82: Probabilities associated with biopsy related complications

Event	Probabilty	PSA distribution	Source
Biopsy complication	0.117	Beta (SE = , alpha = 134 and beta = 1013)	Rosario *et al*. 2012
Probability of hospital admission	0.112	Dirichlet (alpha= 112)	Rosario *et al*. 2012
Reason for hospital admission:		Dirichlet	
- Urinary tract infection related	0.716	(alpha = 716)	Nam *et al*. 2010
- Urinary bleeding related	0.194	(alpha = 194)	Nam *et al*. 2010
- Urinary obstruction related	0.09	(alpha = 90)	Nam *et al*. 2010
Probability of consultation	0.888	(alpha = 888)	Rosario *et al*. 2012
Location of consultation:		Dirichlet	
- GP	0.773	(alpha = 773)	Rosario *et al*. 2012
- Urology Dept. Nurse	0.118	(alpha = 118)	Rosario *et al*. 2012
- Other - NHS Direct	0.109	(alpha = 109)	Rosario *et al*. 2012

Update 2014

B.5.5 Downstream events

The differences in the diagnostic accuracy of the strategies described above will drive differences in the number of patients that are diagnosed in the model, which, in turn, will affect the number of patients that receive treatment or monitoring strategies. Owing to a lack of evidence on different treatments compared against doing nothing, it was assumed that patients receiving radical treatment would follow the progression rates associated with the radical prostatectomy arm of Bill Axelson *et al*. 2011. Thus, in comparison to undiagnosed patients who follow the progression rates associated with the watchful waiting arm of Bill Axelson *et al*. 2011, diagnosed patients that receive radical treatment experience a reduced rate of progression. While this approach was necessary to capture the benefit associated with treated in comparison to doing nothing, it does make the strong assumption that all radical treatments are equally effective.

In terms of the benefits associated with the monitoring strategies, it was assumed that diagnosed patients receiving watchful waiting would have the same progression rate associated with undiagnosed patients (i.e. follow the watchful waiting arm of Bill Axelson *et al*. 2011). Conversely, patients receiving active surveillance were assumed to have a reduced rate of progression, reflecting the fact that only patients at low risk of progression are offered active surveillance. Therefore, the progression rate of patients on active surveillance was estimated by combining data from the radical prostatectomy arm of Bill Axelson *et al*. 2011 with data from an active surveillance study by Klotz *et al*. 2010. It was assumed that patients would follow the time to radical treatment observed in Klotz *et al*. 2010. When moving onto radical treatment, patients were assumed to get the time to local progression associated with radical treatment minus the time that had already been spent on active surveillance.

The proportions of patients receiving each type of treatment were already set in the LSHTM model and were based on a Department of Health National Radiotherapy Advisory group (NRAG) elicitation process. These proportions accounted for the risk stratification of patients and the differing intentions of the treatment and monitoring regimens (i.e. curative or palliative). The proportion of patients receiving each type of therapy is shown in table 83.

Table 83: Treatment proportions in each risk group

Risk groups and treatment proportions	Proportions	PSA distribution
Low risk patients Active surveillance	100.0%	
Intermediate risk patients Radical prostatectomy	26.7%	Dirichlet (alpha = 27)
Radiotherapy	36.7%	(alpha = 37)
Brachytherapy	36.7%	(alpha = 37)
High risk and locally advanced Radiotherapy plus hormones	50.0%	Dirichlet (alpha = 50)
Hormones alone	50.0%	(alpha = 50)
Metastatic **Treatment sequence** Continuous hormones->LHRHa+bicalutamide->dexamethasone->chemotherapy	89.0%	Dirichlet (alpha = 89)
Intermittent hormones->LHRHa+bicalutamide->dexamethasone->chemotherapy	11.0%	(alpha = 11)
Chemotherapy (fourth line) Docetaxel+prednisolone	72.7%	Dirichlet (alpha = 73)
Mitoxantrone+prednisolone	27.3%	(alpha = 27)

Update 2014

While each of the radical treatments was assumed to be equivalent in terms of their effect on progression rates and survival, differences in treatment related morbidity were captured. The three most common adverse events associated with prostate cancer were included in the model; urinary incontinence, sexual dysfunction and bowel dysfunction, with probabilities of occurrence drawn from relevant randomised controlled trials. Table 84 shows the adverse event rates associated with each treatment that were applied in the model along with their reference.

Table 84: Treatment related adverse events applied in the model

Treatment option	Proportions	PSA distribution	Source
Radical prostatectomy Sexual dysfunction	58.0%	Beta (SE = , alpha = 168, beta = 121)	Bill Axelson *et al*. 2011, radical prostatectomy arm
Urinary incontinence	34.1%	Beta (SE = , alpha = 99, beta = 190)	Bill Axelson *et al*. 2011, radical prostatectomy arm
Bowel dysfunction	0.0%	Not varied	Bill Axelson *et al*. 2011, radical prostatectomy arm
Radiotherapy+hormones Sexual dysfunction	74.6%	Beta (SE = , alpha = 250, beta = 85)	Widmark *et al*. 2009, EBRT+Hormones arm
Urinary incontinence	18.1%	Beta (SE = , alpha = 64, beta = 289)	Widmark *et al*. 2009, EBRT+Hormones arm
Bowel dysfunction	11.0%	Beta (SE = ,	Widmark *et al*. 2009, EBRT+Hormones

Treatment option	Proportions	PSA distribution	Source
		alpha = 37, beta = 313)	arm
Brachytherapy Sexual dysfunction	42.0%	Beta (SE = , alpha = 42, beta = 58)	Giberti *et al*. 2009 Brachytherapy arm
Urinary incontinence	80.0%	Beta (SE = , alpha = 80, beta = 20)	Giberti *et al*. 2009 Brachytherapy arm
Bowel dysfunction	0.0%	Not varied	Giberti *et al*. 2009 Brachytherapy arm
Hormones alone Sexual dysfunction	64.2%	Beta (SE = , alpha = 197, beta = 110)	Widmark *et al*. 2009, Hormones only arm
Urinary incontinence	11.6%	Beta (SE = , alpha = 39, beta = 298)	Widmark *et al*. 2009, Hormones only arm
Bowel dysfunction	6.9%	Beta (SE = , alpha = 23, beta = 312)	Widmark *et al*. 2009, Hormones only arm

B.6 Cost data

As the simulation progresses 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 2011-12 prices.

The majority of costs were sourced from NHS reference costs 2011/12 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dose and unit cost information from the British National Formulary (BNF), resource use and cost information from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

Costs for each aspect of the treatment pathway are discussed in detail below.

Update 2014

B.6.1 Biopsy cost

The cost of a 10-12 core TRUS biopsy was sourced from the NHS reference costs using the HRG code associated with 'Minor Endoscopic Prostate or Bladder Neck Procedures (male)' in 'Oupatient procedures' (LB27Z). However, the GDG thought that this cost was substantially underestimated and was likely to have not fully incorporated the pathology costs associated with the procedure. Hence an additional pathology cost component amounting to £112.79 was added to the total TRUS biopsy cost. This pathology cost was based on an estimate from a laboratory manager at the Department of Cellular Pathology at the North Bristol NHS Trust and assumes that two biopsy sites.

Where mpMRIs are used to target biopsies, the biopsy cost is assumed to differ depending on the tumour location (which would be identified under mpMRI). If the tumour is found to be in the posterior region, then patients are assumed to undergo a TRUS biopsy and receive the cost described above[x]. However, if the tumour is found in the anterior region, then patients will undergo a transperineal biopsy as they are better suited to detecting tumours in this

x It has been assumed that there is no cost difference in the TRUS performed in the systematic TRUS biopsy and systematic + MRI biopsy arms

region. The cost of a transperineal biopsy was sourced from the NHS reference costs using the same HRG code as a TRUS biopsy (LB27Z) but this time performed as a 'daycase', reflecting that the procedure will be performed under general anaesthetic. As in the TRUS biopsy cost, an additional pathology cost element was added to the estimate, again assuming two biopsy sites.

Patients that require a third biopsy are assumed to receive a saturation biopsy. As above, this cost is based on HRG code LB27Z performed as a daycase. However, the greater number of cores (20-30) was assumed to result in a larger pathology cost. Thus, the pathology cost has been increased to reflect five biopsy sites rather than two.

Table 85 shows the biopsy costs applied in the model.

Table 85: Biopsy costs applied in the model

Cost element	Cost	PSA distribution	NHS reference cost code (HRG code) and description
TRUS Biopsy cost Biopsy as outpatient procedure	£199.00	Gamma (SE = 114.84, alpha = 3, beta = 66)	LB27Z: 'Minor Endoscopic Prostate or Bladder Neck Procedures (male)' in 'outpatient procedures'
Histopathology	£112.79	Not varied	Based on correspondence with a laboratory manager at the Department of Cellular Pathology at the North Bristol NHS Trust. Assumes two biopsy sites.
Total	**£311.79**		
Transperineal biopsy cost Biopsy as outpatient procedure	£539.61	Gamma (SE = 233.95, alpha = 5, beta = 101)	LB27Z: 'Minor Endoscopic Prostate or Bladder Neck Procedures (male)' as 'daycase'
Histopathology	£112.79	Not varied	Based on correspondence with a laboratory manager at the Department of Cellular Pathology at the North Bristol NHS Trust. Assumes two biopsy sites.
Total	**£652.40**		
Saturation biopsy cost Biopsy as outpatient procedure	£539.61	Gamma (SE = 233.95, alpha = 5, beta = 101)	LB27Z: 'Minor Endoscopic Prostate or Bladder Neck Procedures (male)' as 'daycase'
Histopathology	£281.97	Not varied	Based on correspondence with a laboratory manager at the Department of Cellular Pathology at the North Bristol NHS Trust. Assumes five biopsy sites.
Total	**£821.58**		

Update 2014

B.6.2 Costs of mpMRI

The costs associated with using a T2-MRI+DW-MRI+DCE-MRI sequence to guide the additional biopsy cores in the mpMRI arms were based on a recent HTA report (Mowatt *et al*. 2013). In the HTA, a bottom-up costing approach was adopted with radiographer and radiologist time estimated by radiologists involved in the project and unit costs sourced from the Unit Costs of Health and Social care and capital equipment costs from NHS Grampian. Upon review of these cost estimations, the GDG thought that the consultant radiologist time had been underestimated at 16.67 minutes. Thus, for the purposes of the present model, the cost was re-estimated based on a consultant radiologist time of 45 minutes.

For patients receiving a fusion mpMRI, there is an additional cost component associated with the extra capital equipment and time required to perform the procedure. Capital equipment costs were estimated by first calculating annuitized costs using an initial upfront capital cost of £100,000 (estimated by the GDG), an expected useful lifespan of 7 years (estimated shelf life from manufacturers[y]) and a discount rate of 3.5% per year. Cost per minute estimates were then calculated by following the methodology used by Mowatt *et al*. 2013 when estimating the mpMRI costs (see above). The cost per minute was then multiplied by usage time estimates from the GDG (15 minutes registration after the mpMRI scan is done). In addition, this registration is assumed to be performed by two radiographers and so this cost is also added.

Table 86 shows the cost of the mpMRI sequence applied in the model when cognitive and fusion targeting strategies are used.

Table 86: mpMRI cost estimation

Imaging method	Time per patient (mins)	Cost per hour	Total cost
Radiographer 1	43.33†	£48.33‡	£34.91
Radiographer 2	43.33†	£50.00‡	£36.11
Radiologist – consultant	45.00*	£162.00‡	£121.50
Equipment cost per patient	-	-	£88.42‡
Admin and consumable costs	-	-	£34.62‡
Total mpMRI cost	-	-	**£315.56**
Additional costs associated with fusion mpMRI			
Radiographer 1	15.00†	£48.33	£12.08
Radiographer 2	15.00†	£50.00	£12.50
Equipment cost per patient	-	-	£2.29
Total additional cost of using fusion image registration			**£26.87**

† Time estimates from HTA by Mowatt et al. 2013
‡ Cost estimates from HTA by Mowatt et al. 2013
** Time estimate made by the guideline development group (GDG)*
Note that the costs associated with mpMRI are applied deterministically and not varied in the sensitivity analysis

B.6.3 Biopsy complication costs

As mentioned in the previous section, patients receiving biopsies will be at risk of experiencing biopsy complications. The costs associated with these complications were estimated by following the methodology set out in Mowatt *et al*. 2013 but with costs updated to the relevant price year (2011/12). The updated costs are shown in table 87.

Update 2014

y Hitachi, Biopsee and Elekta

Table 87: Biopsy related complication costs

Event	Updated cost	PSA distribution	Source
Hospitilisation Urinary tract infection related	£433.01	Gamma (SE = 99.61, alpha = 19, beta = 23)	NHS reference costs 2011-12. HRG LA04G
Urinary bleeding related	£526.87	Gamma (SE = 221.56, alpha = 6, beta = 93)	NHS reference costs 2011-12. HRG LB18Z
Urinary obstruction related	£1,023.63	Gamma (based on sum of samples from LB09D and LB15E)	NHS reference costs 2011-12. HRG LB09D and LB15E plus the cost of catheter bags over the course of a month (£19.08)*
Consultation: GP	£43.29	Not varied	Netten and Curits. Unit costs of health and social care.
Urology Dept. Nurse	£78.00	Gamma (SE = 38.26, alpha = 4, beta = 19)	NHS reference costs
Other - NHS Direct	£20.23	Not varied	NHS Direct National Health Service Trust Annual Report and Accounts 2011/2012

** Monthly catheter bag cost based on the daily use of an overnight catheter (£6.47) and the weekly use of a leg bag, apart from in the first week where two leg bags would be required (£12.61)*

Update 2014

For inpatient admissions due to urinary tract infection we applied the NHS reference cost for HRG LA04G (Kidney or Urinary Tract Infections with length of stay 1 day or less). Admission for haematuria was assumed to require insertion of a haematuria catheter for bladder irrigation HRG LB18Z (Attention to Suprapubic Bladder Catheter). Urinary retention was assumed to be temporary and was modelled to incur the cost of inserting and subsequently removing a urethral catheter; Daycase HRGs LB09D (Ureter Intermediate Endoscopic Procedures) and LB15E (Bladder Minor Procedure 19 years and over). It was further assumed that the NHS would incur the daily cost of an overnight catheter bag and the weekly cost of a leg bag (apart from in the first week when two leg bags would be required) over the course of a month.

The cost associated with a GP consultation was derived from the Unit Costs of Health and Social Care with an average GP consultation duration of 11.7 minutes. The cost of a consultation with a urology department nurse was derived from the relevant NHS tariff - non-consultant led follow-up attendance, non-admitted, face to face. The cost per NHS direct contact was derived from the NHS Direct National Health Service Trust Annual Report and Accounts 2011/2012, and was based on the total reported staff wages divided by the number of calls logged.

B.6.4 Radical treatment costs

The costs associated with the radical treatment strategies that patients may receive are shown in table 88. The costs were based on the methodology used in the LSHTM model report but with costs updated to reflect the 2011/12 price year. Costs are separated into ‘one-off’ costs, which are typically associated with the treatment or procedure itself and ‘on treatment’ costs, which patients receive for the duration of their treatment.

Table 88: Treatment strategy related costs applied in the model

Treatment strategy and itemised costs	Cost	PSA distribution	Source
Radical prostatectomy			
'One-off' cost			
Procedure cost	£5,004.56	Gamma (SE = 1542.25, alpha = 11, beta = 475)	NHS reference costs 2011/12 – LB21Z 'Bladder neck open procedures - male' in Elective inpatient HRG data
Urology follow-up	£93.96	Gamma (SE = 20.16, alpha = 22, beta = 4)	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face
First surgical consultation	£144.98	Gamma (SE = 37.94, alpha = 15, beta = 10)	NHS reference costs 2011/12 - General surgery in First attendance non-admitted face to face
Follow-up surgical consultation	£110.09	Gamma (SE = 30.47, alpha = 13, beta = 8)	NHS reference costs 2011/12 - General surgery in Follow up attendance non-admitted face to face
Radiotherapy (+Hormones)			
'One-off' costs			
Radiotherapy Planning	£819.27	Gamma (SE = 309.56, alpha = 7, beta = 117)	NHS reference costs 2011/12 – SC51Z 'Preparation for complex conformal radiotherapy' in 'Radiotherapy Planning: Outpatient'
Radiotherapy delivery	£118.47	Gamma (SE = 36.95, alpha = 10, beta = 12)	NHS reference costs 2011/12 – SC23Z 'Deliver a fraction of complex treatment on a megavoltage machine' in 'Radiotherapy Treatment: Outpatient'
Radiotherapy total	£5,202.66		
Urology follow-up	£93.96	Gamma (SE = 20.16, alpha = 22, beta = 4)	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face
'On treatment' costs			
Annual cost of LHRHa*	£870.86†	Not varied	British national formulary (BNF 65)
Brachytherapy			
'One-off' cost			
Urology follow-up	£93.96	Gamma (SE = 20.16, alpha = 22, beta = 4)	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face

Update 2014

Brachytherapy planning	£933.42	Gamma (SE = 173.48, alpha = 29, beta = 32)	NHS reference costs 2011/12 – SC55Z Preparation for interstitial brachytherapy
Brachytherapy delivery	£691.44	Gamma (SE = 197.74, alpha = 12, beta = 57)	NHS reference costs 2011/12 - SC28Z Deliver a fraction of Interstitial Radiotherapy
Brachytherapy planning and delivery total (average of LDR and HDR brachytherapy)‡	£2,662.03		
Hormones alone **'One-off' cost** Urology follow-up	£93.96	Gamma (SE = 20.16, alpha = 22, beta = 4)	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face
Flutamide	£491.13	Not varied	British national formulary (BNF 65)
'On treatment' costs Annual cost of LHRHa*	£870.86†	Not varied	British national formulary (BNF 65)
Metastatic **First line: Continuous hormones**			
'One-off' cost Urology follow-up	£93.96	Gamma (SE = 20.16, alpha = 22, beta = 4)	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face
'On treatment' costs Annual cost of LHRHa*	£902.88	Not varied	British national formulary (BNF 65)
First line: Intermittent hormones			
'One-off' cost Urology follow-up	£93.96	Gamma (SE = 20.16, alpha = 22, beta = 4)	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face
'On treatment' costs Annual cost of LHRHa*	£601.92	Not varied	British national formulary (BNF 65)
Second line: LHRHa+bicalutamide			
'One-off' cost Urology follow-up	£93.96	Gamma (SE = 20.16, alpha = 22, beta = 4)	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face
'On treatment' costs			

Update 2014

Bicalutamide 50mg	£57.27	Not varied	British national formulary (BNF 65)
Annual cost of LHRHa*	£902.88	Not varied	British national formulary (BNF 65)
Third line: LHRHa* + Dexamethasone			
'One-off' cost Urology follow-up	£93.96	Gamma (SE = 20.16, alpha = 22, beta = 4)	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face
'On treatment' costs Dexamethasone annual cost	£1,982.79	Not varied	British national formulary (BNF 65)
Annual cost of LHRHa*	£902.88	Not varied	British national formulary (BNF 65)
Fourth line (chemotherapy) Docetaxel+prednisolone			
'One-off' cost First clinical oncologist	£159.42	Gamma (SE = 60.06, alpha = 7, beta = 23)	NHS reference costs 2011/12 - Clinical oncology in First attendance non-admitted face to face
Admin complex chemotherapy (1st)	£248.29	Gamma (SE = 102.62, alpha = 6, beta = 42)	NHS reference costs 2011/12 - 'Deliver subsequent elements of a Chemotherapy cycle' in 'Chemotherapy Delivery: Daycase and Regular Day/Night'
'On treatment' costs Admin susbequent chemotherapy	£283.89	Gamma (SE = 110.24, alpha = 7, beta = 43)	NHS reference costs 2011/12 - 'Deliver subsequent elements of a Chemotherapy cycle' in 'Chemotherapy Delivery: Daycase and Regular Day/Night'
Docetaxel three weekly cost	£1,023.00	Not varied	British national formulary (BNF 65)
Prednisolone three weekly cost	£14.79	Not varied	British national formulary (BNF 65)
Mitoxantrone+prednisolone			
'One-off' cost First clinical oncologist	£159.42	Gamma (SE = 60.06, alpha = 7, beta = 23)	NHS reference costs 2011/12 - Clinical oncology in First attendance non-admitted face to face
Admin complex chemotherapy (1st)	£248.29	Gamma (SE = 102.62, alpha = 6, beta = 42)	NHS reference costs 2011/12 - 'Deliver subsequent elements of a Chemotherapy cycle' in 'Chemotherapy

Update 2014

			Delivery: Daycase and Regular Day/Night'
'On treatment' costs Admin susbequent chemotherapy	£283.89	Gamma (SE = 110.24, alpha = 7, beta = 43)	NHS reference costs 2011/12 - 'Deliver subsequent elements of a Chemotherapy cycle' in 'Chemotherapy Delivery: Daycase and Regular Day/Night'
Mitoxantrone three weekly cost	£100.00	Not varied	British national formulary (BNF 65)
Prednisolone three weekly cost	£14.79	Not varied	British national formulary (BNF 65)

** Leuproprelin*
† Given continuously or intermittently in the same proportions received in the first line (i.e. 89% given continuously and 11% given intermittently)
‡LDR calculated as cost of brachytherapy planning plus the cost of one brachytherapy fraction (£1,624.86). HDR brachytherapy is calculated as the cost of brachytherapy planning and the cost of four brachytherapy fractions (£3,669.18).

B.6.5 Radical treatment related adverse event costs

The costs associated with the adverse events that patients may experience while receiving radical treatment are shown in table 89 along with their reference. The costs associated with sexual dysfunction are based on the cost of specialist erectile dysfunction services from NHS reference costs. The costs associated with urinary incontinence were based on the assumption that patients will be continuously managed using containment pads with costs sourced from a recent HTA by Ramsay *et al*. 2012. The costs associated with bowel dysfunction were based on the methodology employed in a recent HTA by Hummel *et al*. 2012, with costs updated to reflect the price year considered in the analysis.

Note that the costs associated with sexual dysfunction and urinary incontinence are applied for the duration of the patients lifetime while the costs associated with bowel dysfunction are 'one-off' treatment costs. After the initial treatment for bowel cancer it is assumed that patients would be able to manage the condition with laxatives. The cost of laxatives was not incorporated in the model because it was considered to be fairly negligible and in many instances may not be incurred by the NHS as they are often bought over the counter.

Update 2014

Table 89: Adverse event related costs applied in the model

Adverse events	Cost	PSA distribution	Source
Sexual dysfunction Specialist erectile dysfunction services	£151.21	Gamma (SE = 25.92, alpha = 34, beta = 4)	NHS reference costs 2011/12
Urinary incontinence Managed by containment pads	£263.60	Not varied	HTA by Mowatt *et al*. 2013
Bowel dysfunction Mean weighted cost that incorporates the costs associated with sigmoidoscopy, laser therapy, enemas and blood transfusion†	£1,611.46	Gamma (calculated as the sum of sampled values from each aspect of the total cost)	HTA by Hummel *et al*. 2010 and NHS reference costs 2011/12

† Uses proportions of patients with Grade 2 and Grade 3 bowel dysfunction reported in a recent HTA by Hummel et al. 2010

B.6.16 Other costs

Update 2014

Other costs associated with the management and monitoring of prostate cancer patients are captured as the model progresses. These costs are shown in table 90. The costs were obtained from the NHS reference costs 2011-12 by applying the relevant HRG code.

Table 90: Other costs applied in the model

Treatment	Mean unit cost (£)	PSA distribution	Source
Urology consultant (1st)	£128.91	Gamma (SE = 35.48, alpha = 13, beta = 10)	NHS reference costs 2011/12 - Urology First attendance non-admitted face to face
Urology consultant (follow up)	£93.96	Gamma (SE = 20.16, alpha = 22, beta = 4)	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face
Surgical consultant (1st)	£144.98	Gamma (SE = 37.94, alpha = 15, beta = 10)	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face
Surgical consultant (follow up)	£110.09	Gamma (SE = 30.47, alpha = 13, beta = 8)	NHS reference costs 2011/12 - General surgery in Follow up attendance non-admitted face to face
Clinical oncology consultant (1st)	£159.42	Gamma (SE = 60.06, alpha = 7, beta = 23)	NHS reference costs 2011/12 - Clinical oncology in First attendance non-admitted face to face
Clinical oncology consultant (follow up)	£113.17	Gamma (SE = 48.08, alpha = 6 , beta = 20)	NHS reference costs 2011/12 - Clinical oncology' in 'Follow up attendance non-admitted face to face
Telephone follow up	£47.36	Gamma (SE = 25.02, alpha = 4, beta = 13)	NHS reference costs 2011/12 - Urology in consultant led follow up non face-to-face
PSA in primary care	£19.60	Not varied	PSA test from Ramsay *et al*. (£5.91), which was sourced from Newcastle upon Tyne Hospitals NHS Foundation Trust. Plus the cost of a consultation with a practice nurse (£13.69) from Unit health and Social care costs.
PSA in secondary care	£19.60	Not varied	PSA test from Ramsay *et al*. (£5.91)19 plus the cost of a consultation with a practice nurse (£13.69), as above.5
CT scan	£92.46	Gamma (SE = 30.15, alpha =9 , beta = 10)	NHS reference costs 2011/12 - Computerised Tomography scan, one area, no contrast, 19 years and over (outpatient)
mpMRI scan for staging prostate cancer	£315.56	Not varied	Mowatt *et al*. 2013 and GDG assumptions. Assumes that a multiparametric T2-DW-DCE MRI sequence would be used to stage the patient (equivalent to that used in diagnosis).
Bone scan	£185.51	Gamma (SE = 75.29, alpha = 6 , beta = 31)	NHS reference costs 2011/12 - Nuclear medicine, category 2 (outpatient)
Flexible sigmoidoscopy (every 5 years)	£174.05	Gamma (SE = 84.68, alpha = 4, beta = 41)	NHS reference costs 2011/12 - Diagnostic flexible sigmoidoscopy 19 years and over (outpatient)

Update 2014

B.7 Effectiveness estimates and health-related quality of life data

The model estimates effectiveness in terms of life years and quality adjusted life years (QALYs). Life years are estimated by adding the time that each patient has spent in pre-defined 'segments' of the model, with each individual patient potentially taking a different path through the model.

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. The utility values chosen for use in the model are consistent with other recent economic evaluations of prostate cancer (Hummel *et al*. 2010 and Mowatt *et al*. 2013). Utility values for undiagnosed and diagnosed localised and locally advanced prostate cancer were sourced from a cohort study of patients undergoing external beam radiotherapy (Korfage *et al*. 2005). It was assumed that patients with locally advanced prostate cancer for more than 52 months would have a utility value associated with that of castrate resistant prostate cancer (CRPC). The utility value associated with metastatic disease was sourced from a sample of 45 to 70 year old males presenting at a primary care medical facility in the US (Volk *et al*. 2004). Table 91 shows the health state utility values applied in the base case analysis.

Table 91: Health state utilities applied in the model

Health state	Utility	PSA distribution	Reference
Localised (undiagnosed)	0.890	Beta (SE = 0.01, alpha = 492, beta = 61)	Korfage *et al*. 2005
Localised (diagnosed)	0.880	Beta (SE = 0.02, alpha = 277, beta = 38)	Korfage *et al*. 2005
Locally advanced (undiagnosed)	0.810	Beta (SE = 0.01, alpha = 582, beta = 137)	Korfage *et al*. 2005
Locally advanced (diagnosed)	0.810	Beta (SE = 0.01, alpha = 582, beta = 137)	Korfage *et al*. 2005
Castrate resistant prostate cancer	0.760	Beta (SE = 0.02, alpha = 329, beta = 104)	Korfage *et al*. 2005
Metastases	0.635	Beta (SE = 0.04, alpha = 91, beta = 35)	Volk *et al*. 2004

In the base case analysis it was assumed that there would be no further decrements associated with adverse events. This reflects the population included in the Korfage *et al*. 2005 who had numerous treatment-related morbidities but nonetheless reported high QoL values. However, the QoL impact associated with adverse events was considered in a sensitivity analysis using the utility decrements shown in table 92 (note that decrements were applied in an additive fashion).

Table 92: Adverse event related utility decrements applied in a sensitivity analysis

Treatment related morbidity	Disutility value	Source
Sexual dysfunction	0.100	Krahn *et al*. 2003
Urinary dysfunction	0.060	Krahn *et al*. 2003
Bowel dysfunction	0.110	Krahn *et al*. 2003

Update 2014

B.8 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 the new cost-effectiveness result.

To further estimate uncertainty in the model, probabilistic sensitivity analysis (PSA) was performed. PSA 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 (informed, where possible, by some measure of variance reported in the relevant study). 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 PSA are shown in each of the input tables in this report. 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.9 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 57.

Figure 57: 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 willingness to pay (WTP) 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.

Update 2014

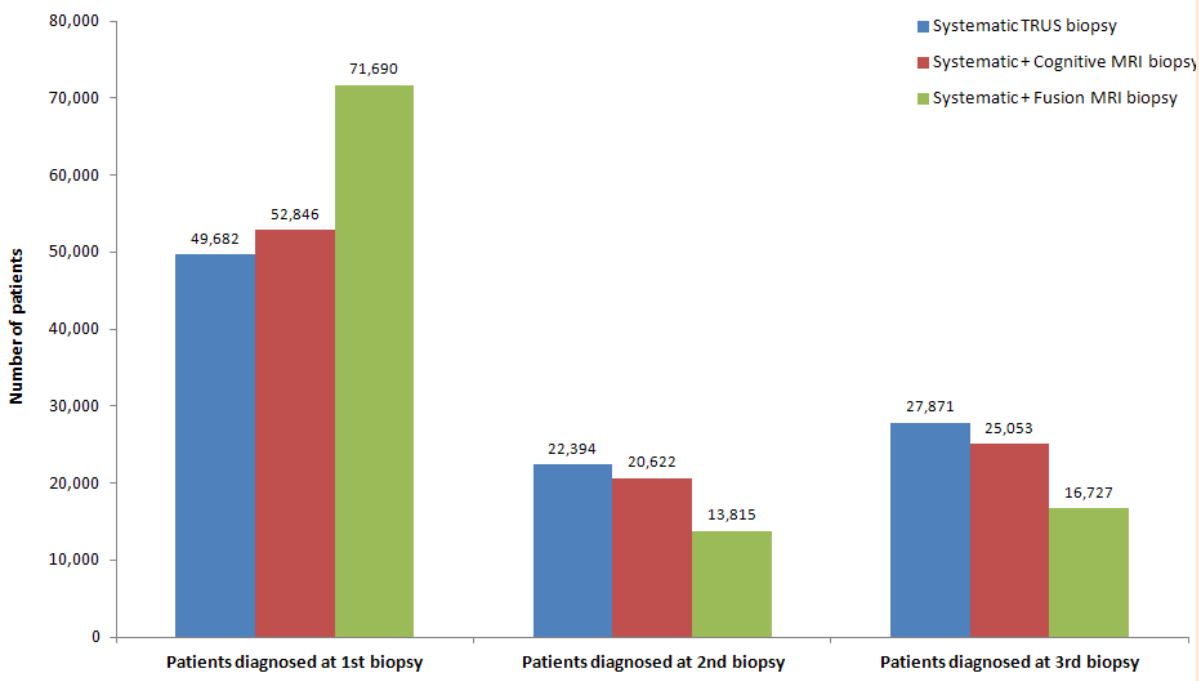
B.9.1 Base case results

The base case results of the model in terms of the number of prostate cancers detected at each biopsy are shown in figure 58. It can be seen that more cancers are detected at the first biopsy when using the systematic plus mpMRI biopsy strategies. However, at the second and third biopsies it can be seen that more cancers are detected when using the TRUS alone strategy. Of course, this is partly a result of more patients remaining undiagnosed after the first biopsy but there is another aspect too. 50% of patients in the TRUS arm are assumed to get a scheduled rebiopsy after 3 months whereas in the mpMRI strategies this is not an option. Thus, patients in the TRUS arm will get another rebiopsy sooner and this increases the number of cancers that can be detected.

The influence of this is particularly striking when observing the total number of cancers detected over the three biopsies; 99,947 detected by TRUS, 98,521 detected by systematic + cognitive mpMRI biopsies and 102,232 detected by systematic + fusion mpMRI biopsies.

Thus, overall, the TRUS arm actually detects more cancers than the systematic + cognitive mpMRI biopsies arm, despite the better sensitivity of the systematic + cognitive mpMRI biopsies arm.

Figure 58: Number of patients diagnosed at each biopsy in the three diagnostic strategies



The base case cost-effectiveness results of the model are presented in table 93. It can be seen that the effectiveness and cost-effectiveness of using mpMRI before a systematic biopsy depends upon the targeting system that is used. The cognitive targeting approach was found to be less effective than systematic TRUS biopsy (8.79 vs 8.81 QALYs) and less costly (£9,897 vs £10,064). This results in an estimated ICER of £7,423 per QALY. Given that both the incremental costs and benefits are negative; this value needs to be interpreted with caution. It implies that, for every QALY lost by using the cognitive targeting strategy, £7,423 is saved. For the strategy to be considered cost-effective, this saving needs to exceed the WTP threshold. Thus, at the commonly accepted WTP threshold of £20,000 per QALY, this strategy would not be considered cost-effective.

The results for the fusion targeting approach were very different as it was found to be more effective (0.009 QALYs) and more costly (£326) than the systematic TRUS biopsy strategy. This results in an estimated ICER of £35,341 per QALY i.e. a systematic + fusion mpMRI biopsy strategy provides one additional QALY at a cost of £35,341, in comparison to systematic TRUS biopsy. Therefore, at a willingness to pay threshold (WTP) of £20,000 per QALY, this strategy would not be considered cost-effective.

Table 93: Base case total expected costs, QALYs and ICER per patient

Treatment option	Total QALYs	Incremental QALYs	Total costs	Incremental costs	ICER
Systematic TRUS biopsy	8.813	-	£10,064	-	-
Systematic + cognitive mpMRI biopsy	8.791	-0.022	£9,897	-£167	£7,423
Systematic + fusion mpMRI	8.822	0.009	£10,390	£326	£35,341

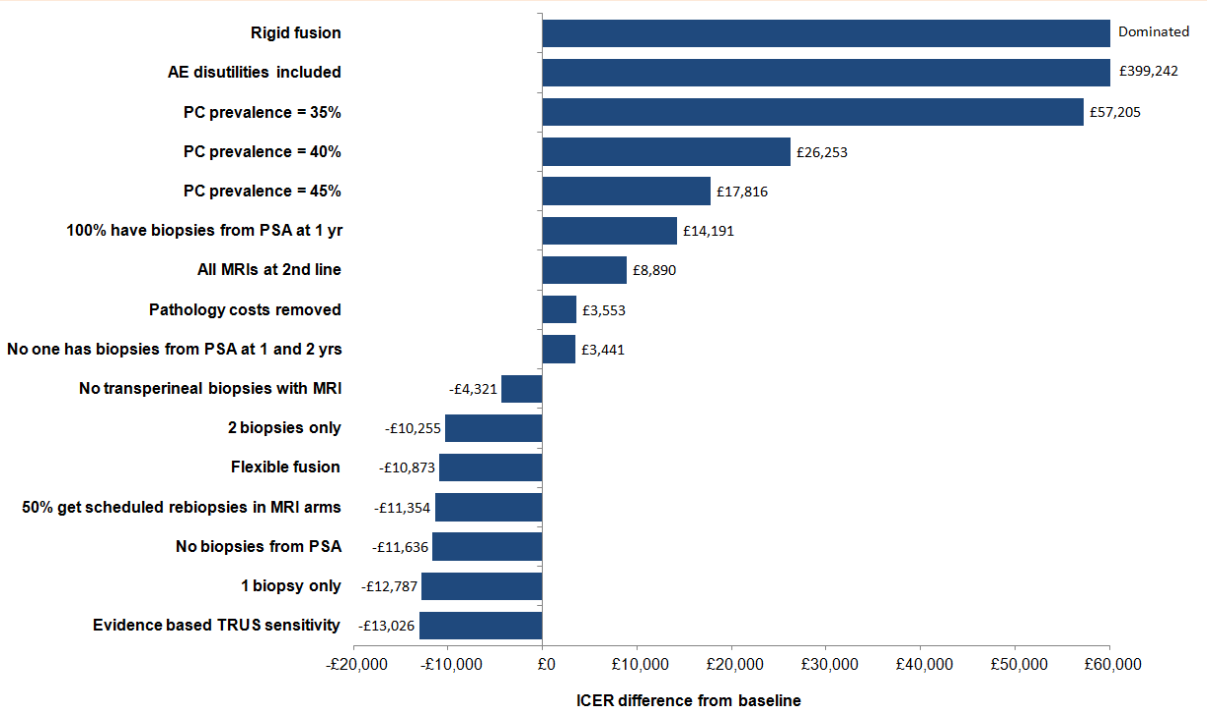
Update 2014

Treatment option	Total QALYs	Incremental QALYs	Total costs	Incremental costs	ICER
biopsy					

B.922 Sensitivity analysis

The results of the one-way sensitivity analysis are shown in figure 59. Note that, given the systematic + cognitive mpMRI biopsy strategy remained the least preferred strategy in all modelled analyses, its results are not presented. Instead the comparison of systematic TRUS biopsy and systematic + fusion mpMRI biopsy is focused upon. The x axis shows the difference in ICER value compared to the base case ICER with the vertical line representing the base case ICER result. Values to the left of the vertical line show that the ICER is lower than in the base case (i.e. more cost-effective) and values to the right of the vertical line show that the ICER is higher than in the base case (i.e. less cost-effective).

Figure 59: Results of one-way sensitivity analysis for comparison of systematic TRUS biopsy and systematic + fusion mpMRI biopsy



The results show that the model is sensitive to numerous input parameters within the model with systematic + fusion mpMRI biopsy found to be nearly cost-effective with an ICER of £22,316 per QALY to be being dominated (i.e. less effective and more costly than systematic TRUS biopsy). However, notably, the ICER value did not fall below a WTP threshold of £20,000 per QALY in any of the modelled scenarios.

The sensitivity analyses on the prevalence of prostate cancer in the modelled population showed this to be a crucial variable. Lower estimations of prevalence were explored and were found to substantially increase the ICER with increases of £17,816, £26,253 and £57,205 per QALY when prevalence was changed to 45%, 40% and 35%, respectively.

The sensitivity analyses also suggest that the type of fusion targeting used (flexible or rigid) could have a significant impact on the cost-effectiveness of the intervention. This analysis was based on the effectiveness data reported by Delongchamps *et al*. 2013 where flexible

Update 2014

targeting was found to considerably improve detection. Thus, when assuming that flexible fusion targeting is used the cost-effectiveness improves considerably (a reduction of £10,873 in comparison to the base case) and when assuming that rigid fusion targeting is used cost-effectiveness considerably worsens to the extent that systematic TRUS + fusion MRI biopsy becomes dominated by systematic TRUS.

Relaxing the assumption that patients receiving MRI would not have the option of a scheduled rebiopsy was also shown to be influential. When assuming that 50% of patients would have a rebiopsy three months after an initial negative biopsy (in-line with assumptions in systematic TRUS arm), the cost-effectiveness improves substantially (a reduction of £11,354 per QALY).

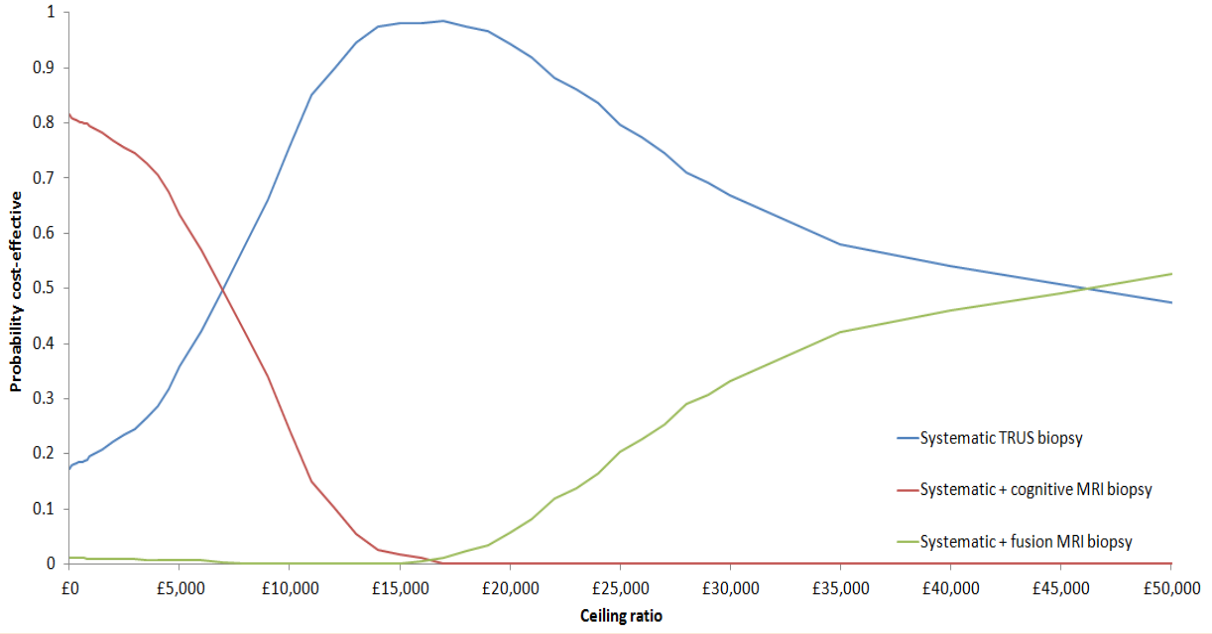
The inclusion of disutilities associated with the radical treatment related adverse events was also found to have a substantial effect. Incorporating these values increased the ICER by £363,901 per QALY, which is a substantial increase. This is essentially because the value of being diagnosed is reduced because the quality of life associated with being treated has been reduced.

Making alterations to the assumptions regarding what happens to patients undergoing PSA monitoring was also found to be influential, although perhaps not to the same extent as changes in some of the other scenarios. In particular, assuming that no patients would leave PSA monitoring for a biopsy was shown to substantially reduce the ICER (a reduction of £11,120 per QALY).

The results of 500 runs of the probabilistic sensitivity analysis are shown in figure 60, which depicts the results using a cost-effectiveness acceptability curve (CEAC). The graph shows the probability of each diagnostic strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis. It provides a useful insight into how parameter uncertainty in the model affects the cost-effectiveness decision.

Update 2014

Figure 60: Cost-effectiveness acceptability curve (CEAC) depicting results of probabilistic sensitivity analysis (PSA) with 500 runs



It can be seen from the CEAC that systematic + cognitive MRI biopsy has the highest probability of being cost-effective at a threshold of zero but this decreases as the threshold increases (up to a threshold of around £7,000 per QALY). Systematic TRUS biopsy then has the highest probability of being cost-effective, with this probability increasing along with the threshold until a threshold of around £16,000 per QALY is reached. Thereafter, the

probability of systematic TRUS biopsy decreases as the probability of systematic + fusion MRI biopsy increases. At the decision threshold of £20,000 per QALY, systematic + fusion MRI biopsy has a 6% probability of being cost-effective while systematic TRUS biopsy has a 94% probability of being cost-effective.

B.9.3 Alternative scenario

An alternative scenario was modelled whereby it was assumed that only targeted cores would be taken at the first biopsy line, under the assumption that patients with a negative MRI would not undergo a biopsy. This was implemented by using the accuracy data associated with targeted biopsies from the clinical evidence review (Moore *et al*. 2013, Haffner *et al*. 2011, Park *et al*. 2011, Belas *et al*. 2012 and Delongchamps *et al*. 2013). The results showed that both cognitively targeted cores and fusion guided cores were less effective and less costly than the systematic TRUS strategy. Neither strategy provided cost savings that were significant enough to make their lower effectiveness acceptable, with ICERs of £16,284 and £16,535 per QALY in the cognitive and fusion targeted MRI strategies, respectively.

These results are not surprising as only performing the targeted biopsies was shown to reduce cancer detection (in comparison to the base case strategy of systematic and targeted biopsies). However, the evidence suggests that those cancers that are not detected by mpMRI are likely to be insignificant cancers. Thus, it is debatable whether it is preferable to detect such cancers as the morbidities associated with treatment might outweigh any benefits of the treatment.

Thus, as a further exploratory analysis, it was assumed that the false negatives in the MRI arms were insignificant cancers. This effect was estimated by assuming that the effectiveness observed in the base case analysis could be maintained but with the lower costs associated with the targeted strategies. This assumption is likely to overestimate the potential benefits of the targeted strategies but nevertheless acts as a useful illustration. The results showed that cognitive targeting was less effective and less costly than systematic TRUS biopsy with an ICER of £27,146. Thus, strictly, cognitive targeting would be preferred to systematic TRUS as it provides enough of a cost reduction to justify its poorer effectiveness. Fusion targeting, on the other hand, was found to be more effective and less costly than systematic TRUS biopsy and so was actually the dominant strategy.

Update 2014

B.10 Discussion and conclusions

This analysis aimed to estimate the cost-effectiveness of mpMRI before TRUS guided prostate biopsy in men with suspected prostate cancer. The results suggest that the cost-effectiveness is highly dependent upon the targeting strategy that is employed when using the mpMRI. The strategy involving cognitive targeting was found to be less effective than a strategy using TRUS as it detected less cancer over the course of three biopsies. The strategy was cheaper than the TRUS strategy but not by enough to make it cost-effective. Thus, the strategy of systematic + cognitive mpMRI biopsy would not be a preferred strategy.

On the other hand, when fusion targeting is used the results are very different. Overall there was an increased detection of prostate cancer and, on average, an earlier time to diagnosis. This manifests itself in better effectiveness outcomes with a modest increase in life years and QALYs. However, it was also more costly than the TRUS strategy, although again the differences were relatively small. Its ICER was estimated to be above the commonly accepted WTP of £20,000 per QALY. Furthermore, in the one-way sensitivity analyses the ICER value was found to remain above £20,000 per QALY in all the modelled analyses. The probabilistic sensitivity analysis showed that, at a threshold of £20,000 per QALY, systematic TRUS biopsy was likely to be the preferred strategy with a 94% probability of being

considered cost-effective. Systematic + fusion MRI biopsy had only a 6% probability of being considered cost-effective at this threshold.

However, the ICER was relatively close to being cost-effective and it is possible that re-evaluating the cost-effectiveness when better evidence becomes available might produce a different outcome. Indeed, the results also suggest that a strategy of only biopsying men with a positive mpMRI scan could be a cost-effective (and indeed dominant) strategy. However, this result was based on a very speculative analysis and would require a full assessment to be confirmed. Furthermore, it seems that further evidence is required to convince clinicians that mpMRI does not miss a substantial amount of significant cancers.

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 analysis, the primary effectiveness data were drawn from studies which did not use a strong reference standard, such as the commonly accepted 'gold standard' of histopathology of radical prostatectomy. Indeed, the strategy that we are considering as the intervention in our analysis was also the reference standard in the studies. Therefore, it was necessary to supplement this data with estimates from the GDG to more accurately reflect the possibility of attaining false negatives.

In addition, the significance of the effectiveness data reported in the studies is hindered by the relatively low patient numbers. This is particularly true in the studies informing the fusion targeted mpMRI strategies (n=264, Delongchamps *et al*. 2013).

Furthermore, as this particular analysis covers the majority of the treatment pathway for prostate cancer patients, other clinical data sources were necessary to fully model the progression of patients. The underlying progression of prostate cancer was assumed to be equivalent to the watchful waiting arm of Bill Axelson *et al*. 2011. This study considered a US population in the pre-PSA testing era and hence may not be fully applicable to the UK setting. In addition, the outcomes in Bill Axelson *et al*. 2011 relate to the point of documented progression rather than the 'true' underlying time of histological change

Update 2014

Patients receiving radical treatment or active surveillance were assumed to get a reduced rate of progression associated with the radical prostatectomy arm of Bill Axelson *et al*. 2011. This was a necessary assumption because the model needed to be based on a comparative data that considered no treatment and treatment. However, clearly this is a substantial simplification and does not account for the possibility of differences in effectiveness between radical treatments.

A further limitation, that is, in many ways, linked to the general uncertainty surrounding the clinical evidence, is that numerous assumptions were necessary to be able to run the analysis. This largely reflects the uncertainty in this area regarding the proportion of men that have prostate cancer (i.e. prevalence) and how they might progress. While every effort has been made to ensure that the assumptions that have been made are reasonable and reflect a conservative approach, it is still not ideal to have an analysis that is highly dependent upon assumptions.

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 particular issue with the present economic evaluation is the extent to which adverse events are incorporated in quality of life estimates. In the base case, it was assumed that the impact of adverse events is already incorporated in the quality of life estimates because numerous patients within the study were suffering from adverse events. However, the quality of life values within this study were relatively high and so it is possible that the full detrimental impact of adverse events has not been accurately captured. This issue was also shown to be an important one in the sensitivity analysis as incorporating adverse event related disutilities had a huge influence on the cost-effectiveness results.

In conclusion, the economic analysis suggests that the cost-effectiveness of biopsying additional cores identified using mpMRI is dependent upon the targeting strategy that is employed. Cognitive targeting was not found to be cost-effective in any of the modelled analyses whilst the cost-effectiveness of fusion targeting was substantially better. However, the ICER associated with fusion targeting was above £20,000 per QALY and so would not be considered cost-effective at the WTP thresholds commonly accepted by NICE.

However, it should be acknowledged that the analysis does suggest that there could be substantial benefits associated with the use of MRI before diagnosis. This is particularly true in the analysis where it was assumed that biopsies would not be performed in patients with a negative mpMRI. In this strategy costly and detrimental (in QoL terms) potentially unnecessary biopsies could be avoided. However, further evidence will be required to convince clinicians that mpMRI does not miss a substantial amount of significant cancers.

Note that the conclusions must also be tempered by the limitations of the analysis. Most notably, the limitations of the clinical evidence upon which the analysis is based and the considerable uncertainty that necessitated that strong assumptions be made in some areas. In general, there appears to be a need for better evidence in this area to be able to better assess the cost-effectiveness of this potentially useful and practice changing intervention.

B.11 References

Belas O, Klap J, Cornud F, *et al*. Prebiopsy multiparametric MRI of the prostate: the end of randomized biopsies?. [French]. Prog.Urol 2012 22(10):583-589.

Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C *et al*. Radical prostatectomy versus watchful waiting in early prostate cancer. 2011;:1708-1717.

Curtis, L. Unit Costs of Health and Social Care 2012, Personal Social Services Research Unit (PSSRU), University of Kent, Canterbury (2010).

Chib S, Greenberg E. Understanding the Metropolis-Hastings Algorithm. The American Statistician 1995;49:327-335.

Delongchamps N, Peyromaure M, Schull A *et al*. Prebiopsy Magnetic Resonance Imaging and Prostate Cancer Detection: Comparison of Random and Targeted Biopsies. J. Urol 2013;189(2):493-499

Fink KG, Hutarew G, Lumper W, Jungwirth A, Dietze O, Schmeller NT. Prostate cancer detection with two sets of ten-core compared with two sets of sextant biopsies. Urology (2001): 58 (5) 735-739

Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. World J Urol 200;27(5):607-12

Haffner, J., Lemaitre, L., Puech, P., Haber, G. P., Leroy, X., Jones, J. S. *et al*. (2011). Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. BJU International, 108, t-8.

Hummel S, Simpson E, Hemingway P, Stevenson MD, Rees A. Intensity-modulated radiotherapy for the treatment of prostate cancer: A systematic review and economic evaluation. Health Technol Assess 2010;14:1-133.

Joint Formulary Committee. British National Formulary (online ed. 65) London: BMJ Group and Pharmaceutical Press <http://www.bnf.org>

Update 2014

Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 2010 ;28(1):126-31

Korfage IJ, Essink-Bot ML, Borsboom GJ, Madalinska JB, Kirkels WJ, Habbema JD *et al*. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Int J Cancer 2005;116:291-6.

Krahn M, Ritvo P, Irvine J, Tomlinson G, Bremner KE, Bezjak A *et al*. Patient and community preferences for outcomes in prostate cancer: implications for clinical policy. Med Care 2003;41:153-64.

Life expectancy at birth, UK, 1980-82 to 2008-2010, UK Interim Life Tables [webpage on the Internet]. London: Office for National Statistics; 2012 [accessed June 2012]. URL:http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2008-2010/sum-ilt-2008-10.html.

Moore CM, Robertson NL, Arsanious N, Middleton T, Villers A, Klotz L, Taneia SS, Emberton M. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol (2013): 63(1)125-40

Mowatt G, Scotland G, Boachie C, Cruickshank M, Ford JA, Fraser C, Kurban L, Lam TB, Padhani AR, Royle J, Scheenen TW, Tassie E. Systematic review of the diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, 2012.

Nam RK, Saskin R, Lee Y, Liu Y, Law C, Klotz LH *et al*. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. J Urol 2010;183:963-8.

NHS reference costs 2011-12 [database on the Internet]. London: UK Department of Health; [accessed March 2013].

Park BK, Park JW, Park SY, *et al*. Prospective Evaluation of 3-T MRI Performed Before Initial Transrectal Ultrasound-Guided Prostate Biopsy in Patients With High Prostate-Specific Antigen and No Previous Biopsy. AJR 2011;197:W876-W881

Ramsay C, Pickard R, Robertson C, Close A, Vale L, Armstrong N. *et al*. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer." Health Technology Assessment 2012;16(41).

Rosario DJ, Lane JA, Metcalfe C, Donovan JL, Doble A, Goodwin L *et al*. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. BMJ 2012;344:d7894.

Serefoglu EC, Altinova S, Ugras NS, *et al*. How reliable is 12-core prostate biopsy procedure in the detection of prostate cancer? Can Urol Assoc J 2013;7(5-6):e293-8

Scattoni V, Raber M, Capitanio U, Abdollah F, Roscigno M, Angiolilli D *et al*. The optimal rebiopsy prostatic scheme depends on patient clinical characteristics: results of a recursive partitioning analysis based on a 24-core systematic scheme. Eur Urol 2011;60:834-41.

Stadlbauer A, Bernt R, Salomonowitz E, Plas E, Strunk G, Eberhardt K. [Health-economic evaluation of magnetic resonance imaging before biopsy for diagnosis of prostate cancer]. Rofo 2011;183:925-32

Update 2014

Volk RJ, Cantor SB, Cass AR, Spann SJ, Weller SC, Krahn MD. Preferences of husbands and wives for outcomes of prostate cancer screening and treatment. J Gen Intern Med 2004;19:339-48.

Whyte S, Walsh C, Chilcott J. Bayesian calibration of a natural history model with application to a population model for colorectal cancer. Medical decision making: an international journal of the Society for Medical Decision Making 2011;625-641

Widmark A, Klepp O, Solberg A, Damber JE, Angelsen A, Fransson P *et al*. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 2009; 2008/12/19:301-308.

Update 2014

Appendix C: TNM Staging for Prostate Cancer[z]

STAGE	SUB-STAGE	DEFINITION
Tumour		**Primary Tumour**
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1		**Clinically inapparent tumour, neither palpable nor visible by imaging**
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy, e.g., because of elevated prostate-specific antigen (PSA)
T2		**Tumour confined within prostate[aa]**
	T2a	Tumour involves one-half of one lobe or less
	T2b	Tumour involves more than one-half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3		**Tumour extends through the prostatic capsule[bb]**
	T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck improvement
	T3b	Tumour invades seminal vesicle(s)
T4		**Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/pr pelvic wall**

STAGE	SUB-STAGE	DEFINITION
Node		**Regional lymph nodes**
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph nodes metastasis
	N1	Regional lymph node metastasis

STAGE	SUB-STAGE	DEFINITION
Metastasis		**Distant metastasis[cc]**
	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Metastasis at other site(s)

Update 2014

z Sobin LH, Wittekind CH, editors (2002) TNM classification of malignant tumours 6th edition. New York: Wiley-Liss

aa Tumour found in one or both lobles by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

bb Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2

cc When more than one site of metastasis is present, the most advanced category is used. pM1c is the most advanced category

Appendix D: An Economic Evaluation of Radical Prostatectomy Versus Alternative Treatment Options for Clinically Localised Prostate Cancer

D.1 Introduction

The aim of this study was to assess the cost-effectiveness of a number of different treatment options for clinically localised prostate cancer.

D.1.1 Existing Economic Evidence

The systematic literature review identified 5 relevant studies. One of these studies (Horwitz *et al*. 1999) compared 3D conformal radiation therapy with conventional techniques, in a US setting, but was only available as an abstract. The most recent study, by Konski *et al*. 2006, was also performed in a US setting, and compared 3D conformal radiotherapy with intensity modulated radiotherapy (IMRT). The main limitation with this study was that differences in treatment effect were estimated using non-randomised studies, and few details of the literature search used to identify the non-randomised studies were provided. That is, people receiving IMRT were assumed to have a 2% lower probability of biochemical failure each year compared to people receiving 3D conformal radiotherapy, but the evidence base to support this notion is weak. The remaining two studies were both performed in the UK (Hummel *et al*. 2003; Calvert *et al*. 2003). Hummel *et al*. (2003) assessed the costs and effects of a number of different treatment options, including active surveillance and radical prostatectomy, from an National Health Service (NHS) cost perspective. However, a core assumption within the analysis was that the treatment options did not differ in terms of slowing the progression of the underlying prostate cancer. Differences in treatment effect were therefore only estimated in terms of expected side- effect profiles, although none of the evidence was derived from randomised trials. While the baseline estimates suggested brachytherapy was cost-effective compared to active surveillance and radical prostatectomy, the authors concluded that this finding was not robust given the significant uncertainty surrounding the relative side-effects of brachytherapy (and other treatments).

The economic evaluation by Calvert *et al*. (2003) compared policies of watchful waiting with radical prostatectomy in 60-year-old men with Gleason scores of 5–7[dd]. Costs were considered from a NHS perspective and survival was adjusted for changes in health-related quality-of-life in terms of the underlying prostate cancer and adverse effects of treatment such as incontinence and impotence. The results of the analysis suggested that watchful waiting was less costly and more effective than radical prostatectomy (that is, it produced more Quality- Adjusted Life-Years [QALYs]). However, it should be noted the number of QALYs gained per patient was almost equivalent suggesting that gains in survival attributable to radical prostatectomy were more than offset by increases in the incidence of post-operative complications.

The evaluation by Buron *et al*. (2007) compared the costs and benefits of (interstitial) brachytherapy with radical prostatectomy for men with a mean Gleason score of approximately 6. The evaluation was performed from a (French) societal perspective using data for almost 550 patients treated in French hospitals collected between 2001 and 2002. The results suggested that the mean societal costs of the two treatment options were similar

dd Calvert *et al*. (2003) did include a third treatment option, a selection-based management option using DNA-ploidy as a marker of disease progression. However, as this option was considered to be experimental, it is not expanded upon in this paper.

(Euros 8,000–8,700) but that side- effect profiles, and hence health-related quality-of-life scores, differed. More specifically, impotence and urinary incontinence were more pronounced after radical prostatectomy, whereas urinary frequency, urgency and urination pain were more prevalent following brachytherapy. However, there were a number of significant limitations with the analysis: 1) changes in health-related quality-of-life were not measured using a utility-based instrument (meaning it is unclear which, if either treatment, was to be preferred on quality-of-life grounds); 2) patients in the study were not randomised to the treatment options and 3) the treatment options were assumed to be clinically equivalent in terms of the progression of the underlying prostate cancer.

In terms of developing the understanding of the cost-effectiveness of the treatment options for men with localised prostate cancer, there are arguably two main limitations with the existing literature. Firstly, only the evaluation by Hummel *et al*. (2003) attempted to assess the cost-effectiveness of more than two treatment options. Secondly, none of the studies incorporates information from the more recently published randomised control trial (RCT) that compares radical prostatectomy versus watchful waiting (Bill-Axelson *et al*. 2005).

D.1.2 Aims

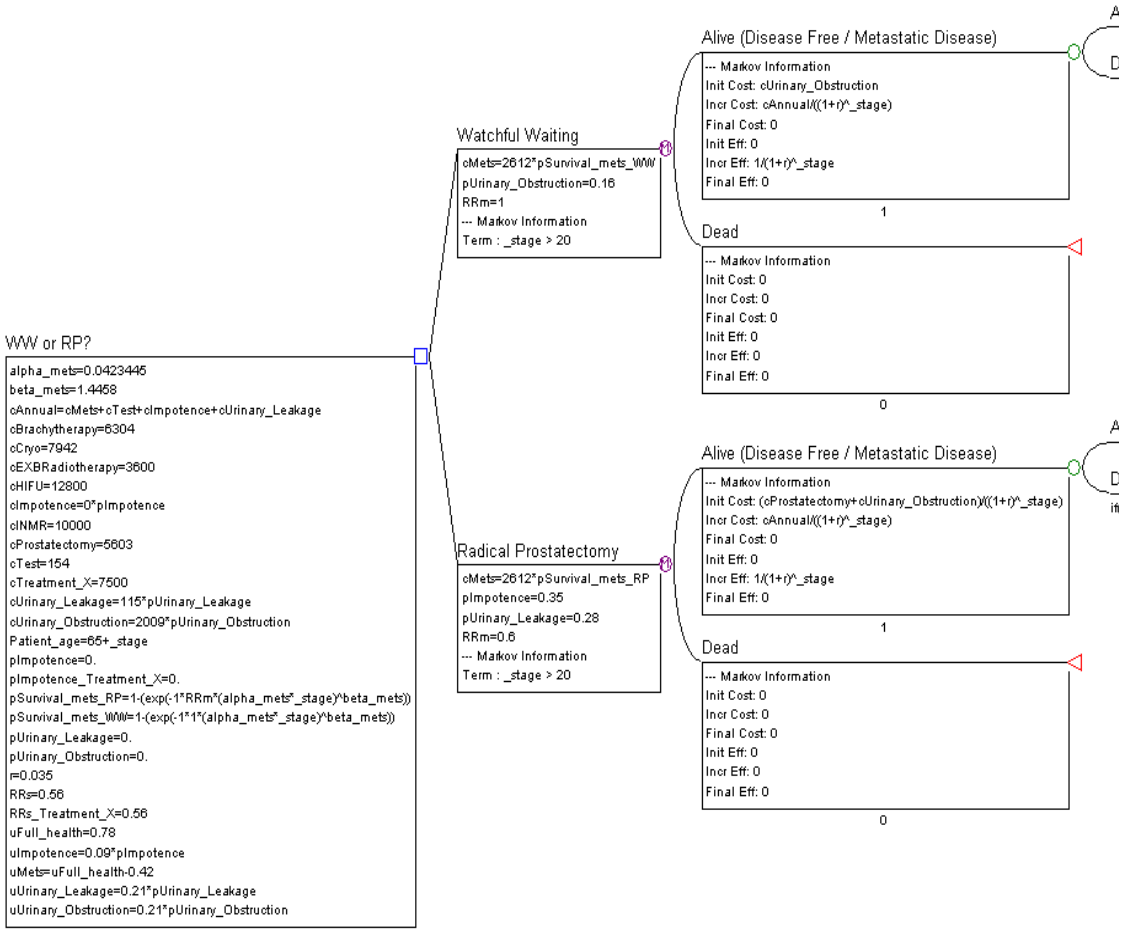
The primary aim of this study was to perform an economic evaluation of watchful waiting versus radical prostatectomy using the 10 year RCT published by Bill-Axelson *et al*. (2005). In the absence of suitable RCT data, a secondary objective was to estimate how effective other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, high intensity focused ultrasound HIFU and cryotherapy) would need to be in order to be considered cost-effective compared by conducting a threshold analysis on the number of additional QALYs that were required to achieve certain willingness to pay thresholds for a gain value of one additional QALY.

D.2 Method

The economic evaluation was based on a Markov model and performed from a NHS cost perspective. Markov models divide a patients' possible prognosis into a series of discrete health states. Costs and benefits are assigned to each health state and transition probabilities define the movement (as a consequence of disease progression and treatment) of an individual between these health states over a particular time frame (cycle length). The costs and benefits of comparative treatments are then estimated on the basis of the length of time individuals spend in each health state.

The original and preferred model structure was to base the economic evaluation on a three-state Markov model (clinically localised disease, metastatic disease and dead), in line with Calvert *et al*. (2003). However, the RCT evidence published in Bill-Axelson *et al*. (2005) did not allow an estimate to be made of the probability of death given metastatic disease. Therefore, a Markov model with only two health states was constructed; alive and dead. The possibility of patients' progressing from clinically localised disease to metastatic disease was contained within the health state 'alive' (Figure 61). This approach represents a mathematical means of staying true to the observed trial (Bill-Axelson *et al*. 2005) while at the same time allowing for disease progression in terms of developing more advanced prostate cancer. An alternative approach would have been to use the three-state Markov model as described above, using estimates of the probability of death given metastatic disease from alternative published sources. However, as the RCT was considered to represent the highest quality data source, this approach was considered to be less appropriate.

Figure 61: Schematic/Programming of Markov Model showing life-years gained as the outcome measure



The model's cycle length was yearly (as the progression of prostate cancer in the model cohort of patients was considered to be relatively slow), and the time horizon for the analysis was 20-years, by which time, the overwhelming majority of hypothetical patients had died. In the base case (the scenario which was considered to be the most likely given all the available evidence and necessary assumptions), hypothetical patients were assumed to have a mean age of 65 years and a modal Gleason score of 5–6, in line with Bill-Axelson *et al*. (2005).

Each cycle, patients allocated to receive watchful waiting or radical prostatectomy had an annual probability of 1) continuing to have localised disease/be cured 2) developing metastatic disease, 3) dying from natural causes or 4) dying from prostate cancer. All patients who developed metastatic disease were assumed to receive hormonal therapy until death. Patients who were allocated to receive radical prostatectomy were assumed to receive surgery on entry to the model. All patients were assumed to receive two prostate specific antigen (PSA) tests per year on an outpatient basis until death.

Three baseline results were generated:

- Cost per additional life-year gained
- Cost per QALY gained (side-effects excluded)
- Cost per QALY gained (side-effects included)[ee].

D.2.1 Transition Probabilities and Treatment Effects

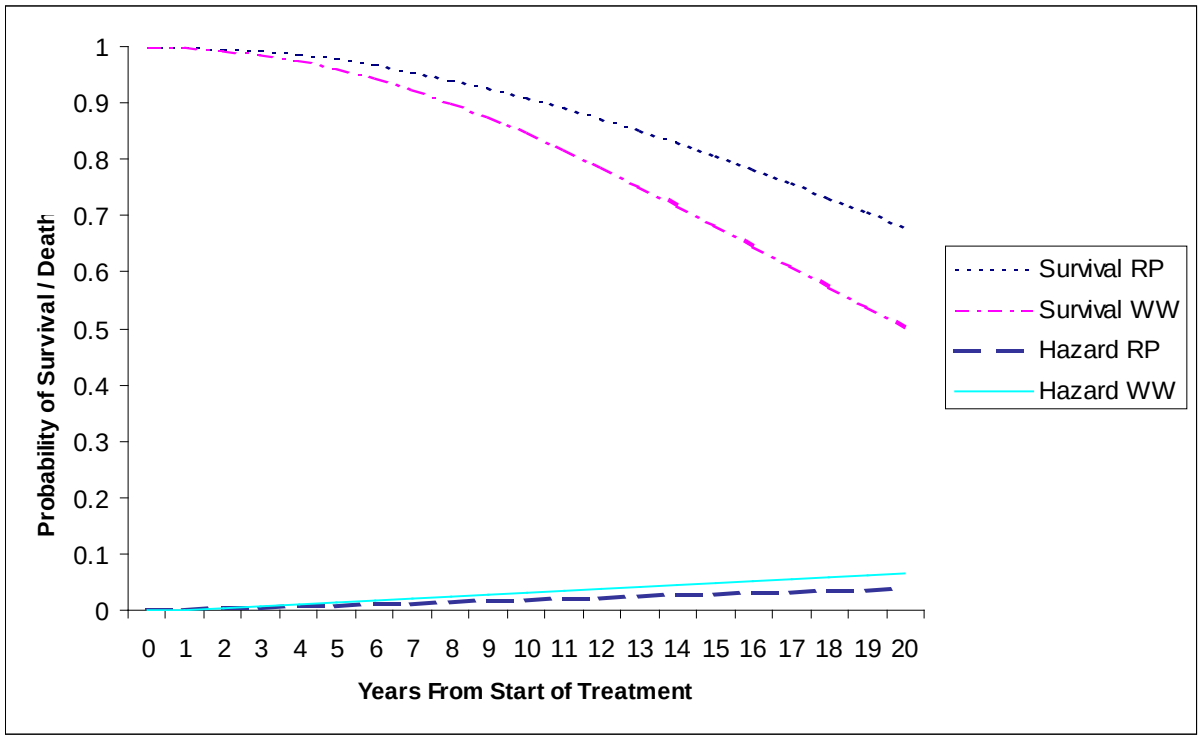
The baseline annual probability of death from prostate cancer for the watchful waiting strategy was taken from Bill-Axelson *et al*. (2005). Standard regression techniques were used to estimate a Weibull function[ff] from the published 10-year Kaplan-Meier disease-specific survival curve (Figure 63). To this was added the annual probability of death from other causes, taken directly from the UK Government's Actuarial Department (http://www.gad.gov.uk/Life_Tables/ eoltable.htm). The annual probability of developing metastatic disease was also estimated from Bill-Axelson *et al*. (2005) by again fitting a Weibull function. However, as a consequence of using a two rather than three-state model, the probability of developing metastatic disease was assumed to be cumulative, and as such, represented at any single point in time, the proportion of patients who were in the health state 'alive' but living with metastatic disease.

ee The latter scenario was taken to represent the main baseline result.

ff A Weibull function is a mathematical method used to estimate the probability of an event happening over time given the observed data. In this instance, it has been used to estimate the probability of death each year.

Figure 62: Reported and extrapolated disease-specific survival curves and hazard functions derived from Bill-Axelson *et al*. (2005).

RP, Radical Prostatectomy; WW, Watchful Waiting



The survival curves are analogous to Kaplan-Meier survival curves. However, the hazard functions relate to the annual probability of death, which increases with increasing time. In both instances, the first 10-years relate to the observed data, whereas years 11–20 relate to the extrapolation.

The effectiveness of radical prostatectomy was modelled by adjusting the baseline probabilities of death from prostate cancer and metastatic disease by the associated relative risks, as published in Bill-Axelson *et al*. (2005) 0.56 (95%CI 0.36–0.88) (Figure 62) and 0.6 (95%CI 0.42–0.86) respectively.

A number of side effects are possible as a result of treatment for prostate cancer. Indeed, the choice of treatment is often based on the anticipated side-effect profiles given the presenting patient, and is therefore an important concern.

In an ideal scenario, the disutility (reduction in health-related quality-of-life) associated with side effects would be derived from randomised studies comparing the relevant treatment options using an appropriate utility-based instrument. A next best solution would be to calculate the proportion of patients in each arm of a RCT that experienced each side effect and to estimate the overall level of disutility by linking this information to relevant published utility weights.

In the context of this modelling exercise, Bill-Axelson *et al*. (2005) did report a selection of side-effects for both the watchful waiting and radical prostatectomy arms. However, utilities were not measured within the trial and specific utility weights were not available for the majority of the reported outcomes (e.g. pain during intercourse).

The main quality of life conclusions from the RCT were published by Steineck *et al*. (over 4 rather than the full 10 years). The authors concluded that erectile dysfunction (80% versus 45%) and urinary leakage (49% versus 21%) were more common in the radical prostatectomy treatment arm whereas urinary obstruction was more common in the watchful waiting arm (44% versus 28%). Levels of bowel function, anxiety, depression and well being

were all reported as being similar across the trial arms. Therefore the following and only assumptions were included in the model with respect to reductions in health related quality-of-life as a result of side-effects: 35% more people receiving radical prostatectomy experienced erectile dysfunction and 28% more people experienced urinary leakage compared to watchful waiting. It was also assumed that 16% more people in the watchful waiting arm experienced urinary obstruction compared to those receiving radical prostatectomy. In the main baseline scenario, the side effects were assumed to occur at the beginning of the model and to be permanent. Sensitivity analysis was used to test the robustness of the results to these and other assumptions.

D.2.2 Health-Related Quality-of-Life (HRQoL)/Utility Weights

The systematic literature review revealed that there have been a reasonable number of HRQoL studies involving men with prostate cancer. However, relatively few have reported utilities, which are required to incorporate HRQoL into economic evaluations in order to estimate Quality-Adjusted Life-Years (QALYs). Therefore, it was assumed that men aged 65 years with localised disease had levels of health equivalent to the general population. Using the UK EQ-5D dataset (Dolan P, 1997), this is equivalent to a utility[gg] value of 0.78[hh]. The utility value associated with metastatic disease was taken from Cowen *et al*. (1999) as 0.42. Cowen *et al*. (1999) also reported a number of utility scores with respect to treatment-related side-effects for localised prostate cancer; a mean of 0.69 for impotence (taken herein to be equivalent to sexual dysfunction) and 0.57 for incontinence (taken herein to represent both urinary obstruction and leakage)[ii].

Further simplifying assumptions were required to operationalise the model with respect to incorporating reductions in health-related quality-of-life as a consequence of side effects. Specifically, a disutility weight was calculated for the three possible side effects by subtracting the side-effect specific utility from the utility value for localised disease:

Disutility for impotence = 0.78 – 0.69 = 0.09

Disutility for urinary obstruction / leakage = 0.78 – 0.57 = 0.21

The disutility weights were also assumed to be additive, meaning for example, that a man with localised disease, with impotence and urinary obstruction experienced a utility of 0.48 (0.78 –0.09 – 0.21). Whereas, for a man with metastatic disease with impotence but no urinary obstruction, the utility value was 0.33 (0.42 – 0.09).

D.2.3 Costs

Costs were only considered from a NHS's perspective. The costs of treatment and PSA testing were taken from published sources, mostly Hummel *et al*. (2003), Calvert *et al*. (2003) and the NHS Cost Index (Table 94). The costs of complications associated with treatments for localised prostate cancer have not been well documented, therefore the following assumptions were made. For urinary obstruction, all men were assumed to receive a transurethral resection of the prostate (TURP). An annual cost of treating incontinence was also included, although it is noted that the study from which this value was taken relates to men with severe urinary storage problems and was not prostate-cancer specific; no published costs for urinary problems in men with prostate cancer could be identified.

gg Utility values of 0 and 1 are taken to equal death and perfect health respectively. States of health between death and perfect health are therefore taken to have utility values somewhere between these two points.

hh A number of utility values representing clinically localised prostate cancer were available, however, they were not adjudged to differ significantly from 0.78 and were not always UK specific.

ii Cowen *et al*. (1999) derived these values in 31 individuals using the time-trade off method.

Table 94: Unit cost estimates

Cost	Estimate	Source
Radical Prostatectomy	£5603	Calvert *et al*. (2003)
Hormonal Therapy (annual)	£2612	Hummel *et al*. (2003)
Transurethral Resection (elective)	£2009	NHS Unit Costs*
Urinary Incontinence	£115 (per annum)	Turner *et al*.^
Twice yearly PSA testing	£154	Calvert *et al*. (2003)
External Beam Radiotherapy (30 fractions)	£3600	NHS Unit Costs (@£120 per fraction)
Two Phase Intensity Modulated Radiotherapy	£10000	Assumption
Brachytherapy	£6304	Hummel *et al*. (2003)
Cryotherapy	£7942	Hummel *et al*. (2003)
HIFU	£7500	EDAP-TMS – quoted in comments on consultation draft

**One-off cost*
^These costs relate to UK individuals with 'significant urinary storage problems', and are not prostate-cancer specific.

Where necessary, costs were inflated to 2006 prices using the Hospital and Community Health Services (HCHS) Pay and Prices Index.

D.2.4 Discounting

In the base case analysis, costs and health outcomes were both discounted at 3.5% per annum in line with NICE recommendations (NICE 2004).

D.2.5 Sensitivity Analysis

A number of one-way sensitivity analyses (where one input variable is changed, the model re-run and a revised incremental cost effectiveness ratio (ICER) calculated) were undertaken to highlight the variables that were the most important in terms of determining the cost-effectiveness of treatment.

Threshold analysis was also undertaken to determine how effective, in terms of additional QALYs, other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to be, to be considered cost-effective com- pared to watchful waiting. Threshold analysis is undertaken by fixing the threshold willingness to pay for an extra unit of health outcome, and determining the size of health benefit survival required to produce an ICER equal to this willingness to pay value[jj]. NICE does not have an absolute level indicating cost-effectiveness. However, NICE's method document suggests that technologies with ICERs above £30,000 per additional QALY are unlikely to be considered cost-effective in the absence of 'robust' evidence (NICE 2007). Therefore, £30,000 per additional QALY was taken to represent the threshold willingness to pay.

jj An incremental cost-effectiveness ratio (ICER) is calculated by dividing the difference in health benefits (in this instance, additional life- years or QALYs) between the different treatment options, into the difference in costs.

D.3 Results

The baseline results are shown in Table 95. The results show that radical prostatectomy costs approximately £4400 more than watchful waiting, but that radical prostatectomy produces an average discounted increase in life expectancy of 0.5 years. This is equivalent to an ICER of approximately £9000 per life-year gained. When no post-operative complications were assumed, radical prostatectomy was also associated with approximately 0.5 extra QALYs, with an associated ICER of £7918. However, when treatment related side effects were assumed to occur, as described in the methods section, radical prostatectomy was 'dominated' by watchful waiting (the main baseline result). That is, radical prostatectomy was more costly and less effective than watchful waiting.

Table 95: Baseline incremental cost-effectiveness ratios

	Cost	LY	QALYs*	QALYs^
WW	£6185	9.69	6.96	6.63
RP	£10619	10.19	7.52	6.36
ICER		£8868	£7918	Dominated

RP, Radical Prostatectomy; WW, Watchful Waiting; ICER, incremental cost-effectiveness ratio.
In QALYs, there is 0 probability of complications following treatment whereas in QALYs^, the additional probabilities of urinary obstruction, urinary leakage and impotence are assumed.*

The figure in bold represents the main baseline result. In this instance, RP is more costly and less effective than WW, thus it is 'dominated'.

D.3.1 Sensitivity Analysis

Sensitivity analysis was performed with respect to the scenario that assumed the possibility of side effects (i.e. the main baseline result). Analysis showed that the baseline ICER was not sensitive to changes regarding, the costs of watchful waiting or the costs of metastatic disease. However, the ICER was found to be extremely sensitive to differing assumptions regarding the possible side effects associated with radical prostatectomy and watchful waiting. For example, when the additional proportion of people undergoing watchful waiting who experienced urinary obstruction was assumed to increase to 40% (from 16%), the ICER was found to be £20,155 per QALY if radical prostatectomy was used instead of watchful waiting. Thus, radical prostatectomy under this assumption appears to be a lot more cost-effective than under the baseline assumptions. The ICER was similarly sensitive to the probability of urinary leakage.

For example, when the probability of urinary leakage following radical prostatectomy was assumed to be 9%, the ICER equalled £30,000 per additional QALY. However, because the disutility associated with impotence was relatively small (0.09) compared to the disutility associated with urinary problems (both 0.21), the baseline results were not so sensitive to the probability of people becoming impotent post-surgery.

The side effect data from the Bill-Axelson *et al*. (2005) are only published in detail after a mean follow-up period of 4-years. When it was assumed that all treatment related side effects resolved after 4 years, the main baseline ICER was £33,926 if radical prostatectomy was used instead of watchful waiting.

One-way sensitivity analysis also showed that the baseline ICERs were relatively sensitive to the cost of radical prostatectomy. However, only when the cost reduced to under £1000 per patient (equivalent to 18% of its original costs), was it judged to be cost-effective compared to watchful waiting at the £30,000 per QALY gained level.

The baseline model did not include the possibility of patients developing hormone-relapsed prostate cancer. However, as a proxy, a threshold analysis was undertaken to demonstrate how costly treatment for hormone-relapsed prostate cancer would need to be for radical

prostatectomy to be cost-effective (at the £30,000 per QALY gained level) compared to watchful waiting. This value was found to be approximately £30,000 per year. Considering the costs quoted in a recent NICE Assessment Report for using docetaxel in combination with a steroid, a cost of £30,000 per year is highly unlikely (http://guidance.nice.org.uk/page.aspx?o=285230).

The baseline ICER was shown to be sensitive to the relative risk of survival. However, only when the relative risk was reduced to approximately 0.04 (from 0.56), was radical prostatectomy cost-effective at the £30,000 per QALY gained level. Given the lower 95% confidence interval reported by Bill-Axelson *et al*. (2005) of 0.36, this scenario is considered to be unlikely.

No sub-group specific relative risk of survival was reported by Bill-Axelson *et al*. (2005) for people with more advanced disease (higher Gleason scores), as it was not found to be a significant predictor of disease-specific mortality. However, disease-specific mortality was shown to differ by age. One-way sensitivity analysis showed that expected costs and QALYs for the two different treatment options differed markedly when different starting ages were assumed. However, in all instances, radical prostatectomy remained the dominated option.

In the absence of suitable RCT data, an estimate was made of the relative risk of disease-related survival that would be required for men with Gleason scores above 6. This was attempted by assuming men with Gleason scores above 6 had double the baseline risk of cancer related death compared with those enrolled in the Bill-Axelson RCT (Bill-Axelson *et al*. 2005). To achieve a threshold willingness-to-pay per QALY gained of £30,000, a relative risk of approximately 0.4 was required. When the baseline risk was quadrupled, this relative risk increased to approximately 0.59, which is above the original baseline relative risk as reported by Bill-Axelson *et al*. (2005).

Threshold analysis was also conducted in order to calculate how many QALYs the various other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to produce in order to be cost-effective[kk].

The original intention was to perform this analysis in relation to the expected costs and QALYs of treating men with radical prostatectomy. However, since in the main baseline result, radical prostatectomy was dominated by watchful waiting, this would have been nonsensical, as it is not considered to be an economically relevant option in the first instance. Therefore, threshold QALYs were calculated in relation to watchful waiting (using a threshold willingness-to-pay of £30,000 per additional QALY).

The results from the threshold analysis showed that relatively modest gains in QALYs are required over 20 years if any of the listed treatments are to be considered cost-effective (Table 96). For example, external beam radiotherapy cost an additional £2103 than watchful waiting (£8288–6185), meaning that 0.07 QALYs are required to make it cost-effective compared to watchful waiting, over a 20 year period. For IMRT, the most costly option at £14688, the equivalent value was 0.29 QALYs, or an additional 4.3 months of perfect health over 20 years.

kk The main assumption underpinning this analysis is that these treatments have been assumed to be equally effective as radical prostatectomy in terms of slowing the progression of the underlying cancer. Thus, any results are contingent on this assumption

Table 96: Results from the threshold analysis over a 20 year period compared to watchful waiting

Treatment	Expected cost of treatment	Required QALY increase*	Equivalent health gain in months^
External beam	£8288	0.07	1
Brachytherapy	£10992	0.16	2
HIFU	£12188	0.20	2.4
Cryotherapy	£12630	0.21	2.6
IMRT	£14688	0.28	3.4

**Required to achieve a cost per QALY gained of £30,000 compared with Watchful Waiting.*
^For example, external beam radiotherapy would have to produce 1 extra month of perfect health over a 20 year period compared to watchful waiting for it to be considered cost-effective, which is itself equivalent to 0.07 QALYs. This was calculated as follows: 1 day of perfect health = 1/365 = 0.002739. 0.07 QALYs / 0.002739 = approximately 1 month.

D.4 Discussion

The primary aim of this study was to perform an economic evaluation of watchful waiting versus radical prostatectomy using the 10 year RCT published by Bill-Axelson *et al*. (2005) (in men with Gleason scores of 5–6). The results suggest that the cost-effectiveness of radical prostatectomy is highly dependent on the choice of health outcomes included in the analysis. If only patient survival is considered, then radical prostatectomy is arguably cost-effective. However, when quality-of-life considerations with respect to both the underlying prostate cancer and treatment-related side effects are included, watchful waiting becomes the dominant option. These results are in line with conclusions drawn by Calvert *et al*. (2003). The sensitivity analysis, however, showed that the results were not robust to certain assumptions, specifically surrounding the health-related effects and treatment-related side-effects; a conclusion also drawn by Hummel *et al*. (2003). Importantly, the results suggest that the cost-effectiveness of radical prostatectomy (and all treatments for that matter) is more dependent on the side-effect profiles than the relative risk of disease progression. Therefore, in order to be able to draw firmer conclusions regarding the cost-effectiveness of radical prostatectomy, more needs to be known about the relative probabilities of the side-effects, their duration and impact on HRQoL.

In the absence of RCT data, threshold analyses were undertaken to calculate how many additional QALYs other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to produce in order to be cost-effective at a £30,000 per additional QALY level. Radical prostatectomy was ruled out as an option, therefore these QALY gains were calculated with respect to watchful waiting. The results suggest that relatively modest improvements are required for these treatments to be cost- effective. For example, external beam radiotherapy only needed to generate an extra 0.07 QALYs over a 20 year period compared to watchful waiting for it to be considered cost- effective. This is equivalent to approximately one extra month of perfect health. For IMRT, the most costly option, the equivalent figure was 3.4 months. Thus while the absence of RCTs prevents a robust economic evaluation of these ‘newer’ treatments, it is possible to conclude that the scope for them to cost-effectiveness is relatively large. Indeed, it is feasible that they could be cost-effective even if it is proved that their greatest impact is on improving the side effects more commonly associated with the ‘older’ treatments. In the mean time, decision-makers will need to judge how likely it is that these QALY gains will be realised.

There are a number of limitations with this economic evaluation. Firstly, the cost-effectiveness of active surveillance has not been estimated. This is partly because active surveillance has not been subject to a RCT but also because modelling its cost-effectiveness would require a much more complicated model. Assuming that PSA testing is the favoured method of monitoring for progressive disease, PSA levels would themselves need to be

modelled, pre and post treatment, rather than cancer stages as has been performed herein. However, the relative effect of treatment on PSA would still be uncertain given the absence of RCT data. Therefore, even if it could be concluded that radical prostatectomy is cost-effective compared with watchful waiting, it is unclear whether it is cost-effective compared with a policy of active surveillance. Similarly, it is also unclear how cost-effective watchful waiting would be compared to active surveillance. Ultimately, however, the cost-effectiveness of active surveillance is likely to depend on a combination of the proportion of men who develop progressive disease, the ability to accurately detect progressive disease and treatment efficacy in men with progressive disease.

A second limitation was that a robust sub-group analysis was not performed for men with differing Gleason scores. This is typically performed using a sub-group specific relative risk of disease progression derived from RCTs and using a sub-group specific relative risk of death. However, this information was not available, and indeed was reported by Bill Axelson *et al*. (2005) not to be statistically significant at the 5% level in a pre-planned sub-group analysis. However, as an indicator to cost-effectiveness, the baseline risks of death were doubled and quadrupled for men with Gleason scores of >6, in order to ascertain how effective treatment should be in terms of preventing deaths in order to be cost-effective. The results showed that when the baseline risk of prostate-specific death was quadrupled, and a relative risk akin to the value reported by Bill-Axelson *et al*. (2005) was assumed, radical prostatectomy was cost- effective at the £30,000 per QALY gained level. However, it is unclear how plausible a relative risk estimate this is in the absence of RCT data in this patient group.

The major conclusion that can be drawn from this evaluation is that the cost-effectiveness of all the modelled treatment options for men with clinically localised prostate cancer is highly dependent on the side effects (and therefore reductions in HRQoL) associated with each of the treatments. Indeed, the baseline assumptions suggest that radical prostatectomy should not be an option for people with Gleason scores of <6 because of its associated post-operative complications. However, different assumptions regarding side effect profiles dramatically altered the findings. Thus, future studies that attempt to quantify these relative side-effect profiles would help to produce more accurate estimates of cost-effectiveness.

D.5 References

Bill-Axelson, A., *et al*. (2005) Radical prostatectomy versus watchful waiting in early prostate cancer. New England Journal of Medicine. 352(19): 1977–1984.

Buron C; Le Vue B; Cosset J-M; Pommier P; Peiffert D; Delannes M; Flam T; Guerief S; Salem N; Chauvenic L and Livartowski A. (2007) Brachytherapy versus prostatectomy in the localized prostate cancer: results of a French multicenter prospective medico-economic study. International Journal of Radiation Oncology, Biology, Physics 67(3): 812–822.

Calvert, N.W., *et al*. (2003) Effectiveness and cost-effectiveness of prognostic markers in prostate cancer. British Journal of Cancer 88(1): 31–35.

Cowen, M.E., *et al*., (1999) The value or utility of prostate cancer states. Journal of Urology 155: 376. Dolan P (1997) Modelling valuations for EuroQol health states. Medical Care, 35:,095–1108

Horwitz, E.M. and A.L. Hanlon, The cost effectiveness of 3D conformal radiation therapy compared with conventional techniques for patients with clinically localized prostate cancer. International Journal of Radiation Oncology, Biology, Physics 1999. 45(5): p. 1219–125.

Hummel, S., *et al*., Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: A systematic review. Health Technology Assessment 2003. 7(33).

1 Konski A *et al*. (2006) Using decision analysis to determine the cost-effectiveness of
2 intensity-modulated radiation therapy in the treatment of intermediate risk prostate cancer.
3 International Journal of Radiation Oncology, Biology ,Physics 66(2): 408–415.

4 National Institute for Clinical Excellence (2004) Guidance for manufacturers and sponsors.
5 London: National Institute for Clinical Excellence.

6 National Institute for Health and Clinical Excellence (2007). The guidelines manual. London:
7 National Institute for Health and Clinical Excellence.
8

Appendix E: The cost-effectiveness of HDR brachytherapy in combination with external beam radiotherapy in comparison to external beam radiotherapy alone

E.1 Introduction

Radiotherapy can be delivered to the prostate in two ways; either by external beam radiotherapy (EBRT) using external x-ray beams from a linear accelerator or by brachytherapy, which involves placing radiation sources directly into the prostate gland. Brachytherapy has become accepted as a standard of care for localised prostate cancer with two forms of brachytherapy typically used in clinical practice; low dose rate (LDR) using permanent seeds or high dose rate (HDR) using temporary implants.

The role of brachytherapy in locally advanced or high risk disease is less clear though. Recently published randomised trials have established that, in patients with locally advanced prostate cancer, EBRT (in combination with hormone therapy) is now standard treatment. However, it has been postulated that brachytherapy may also have a role to play in this group.

Theoretically brachytherapy can deliver a higher dose than EBRT as it does not traverse normal tissues to reach the prostate. However it does not deliver significant radiation dose outside the prostate capsule which may be a significant limitation in high risk and locally advanced disease where extracapsular extension is more prevalent. Hence, a combination of brachytherapy (either LDR or HDR) and EBRT may be optimal.

Update 2014

E.1.1 Aims

This economic evaluation aimed to assess the cost-effectiveness of LDR or HDR brachytherapy in combination with external beam radiotherapy. The analysis considered the perspective of the National Health Service (NHS).

E.2 Existing Economic Evidence

A systematic literature review was performed to assess the current economic literature in this area. The review identified 827 possibly relevant economic papers relating to prostate cancer but none were found that sufficiently addressed the current decision problem.

However, a currently unpublished report on the use of full pathway models in guideline development included an analysis that does address the decision problem. This analysis was conducted by the London School of Hygiene and Tropical Medicine (LSHTM) and is based on the same model that was adapted to investigate the use of MRI before initial biopsy (see Appendix B). The analysis was one of numerous ‘guideline style’ decision problems that were evaluated using the model, with the aim being to test the feasibility of using full pathway models in guideline development.

The analysis conducted by the LSHTM estimated the cost-effectiveness of four alternative treatment options in men with localised or locally advanced, intermediate or high risk prostate cancer; HDR brachytherapy plus EBRT, LDR brachytherapy plus EBRT, brachytherapy alone and radiotherapy plus hormone therapy. The results suggested that brachytherapy monotherapy was the most cost-effective treatment, providing the highest expected QALY gain and the lowest cost. All other options were found to be dominated by this strategy.

However, the modelling exercise was primarily intended to be illustrative and as such there are limitations with the analysis. Most notably, the clinical data used to inform the effectiveness of the interventions were drawn from disparate sources and were sometimes at odds with the directly comparable data available. For instance, efficacy data for EBRT in combination with HDR brachytherapy was drawn from an RCT by Sathya *et al*. 2005, while efficacy data for EBRT alone was drawn from another RCT by Widmark *et al*. 2009. When using this data comparison, EBRT alone was found to be more effective than EBRT In combination with HDR brachytherapy. However, this is in contrast to the directly comparable data from Sathya *et al*. 20051 where EBRT in combination with HDR brachytherapy was found to be more effective than EBRT alone. Furthermore, in the case of LDR brachytherapy there was no RCT evidence available and as such the analysis was based on observational data.

E.3 De Novo Economic Evaluation

Since the economic analysis in its original form did not adequately address the decision problem, the model was adapted and an updated analysis was performed. The primary changes were made to the clinical evidence used to inform the effectiveness of the interventions and to the costs used in the analysis, which were updated to reflect a more recent price year (2011/12).

E.4 Clinical effectiveness data

The results of the clinical evidence review were used to inform the efficacy of the interventions in the model. Since no high quality evidence was identified on the use of LDR brachytherapy in combination with EBRT, this intervention was not modelled. Instead, the analysis was focused on the areas where RCT evidence was available.

Moderate quality evidence from two RCTs (Sathya *et al* 2005 and Hoskin *et al* 2012) suggested that biochemical failure free survival was improved when men were treated with EBRT in combination with HDR brachytherapy compared to EBRT alone (pooled HR = 0.57, 95% C.I. 0.41 to 0.79). In terms of overall survival, there was no clear difference observed between treatment options, with a high degree of uncertainty in the estimates from Sathya *et al*. 2005 and Hoskin *et al*. 2012 (pooled HR = 1.44, 95% C.I. 0.87 to 2.40).

In terms of treatment related morbidity, there was low quality evidence about the relative rates of gastrointestinal and genitourinary complications. Sathya *et al*. 2005 and Hoskin *et al*. 2012 showed that gastrointestinal complications occurred in 6% of men treated with EBRT in combination with HDR brachytherapy and 4% of men treated with EBRT alone (Sathya *et al* 2005 and Hoskin *et al* 2012). Genitourinary complications were found to occur in 22% of men treated with EBRT in combination with HDR brachytherapy and 19% of men treated with EBRT alone (Sathya *et al* 2005 and Hoskin *et al* 2012).

However, it should be noted that, although these RCTs provide the best evidence currently available, they do lack some applicability to current practice. Both studies used lower doses in their EBRT-only arms (66 Gy and 50 Gy respectively) (Sathya *et al* 2005 and Hoskin *et al* 2012) than the minimum of 74 Gy recommended in the 2008 NICE prostate cancer guideline.

E.4.1 Biochemical relapse - modelling approach

The LSHTM model was already ‘pre-loaded’ to run analyses using data from Sathya *et al*. 2005 and Hoskin *et al*. 2007 with time to biochemical failure[ll] in each of the RCTs modelled individually (i.e. as separate scenarios). Thus, for the purposes of this analysis, we used the pre-loaded distributions for time to biochemical failure in patients treated with EBRT plus

ll Biochemical failure was defined in the studies as PSA failure, overt metastatic disease, significant biochemical failure that required hormonal intervention or death as a result of prostate cancer

Update 2014

HDR brachytherapy and EBRT alone from Sathya *et al*. 2005 and Hoskin *et al*. 2007. Figures 63 and 64 show the biochemical relapse-free survival curves that were used in scenario 1 (Sathya *et al*. 20052) and scenario 2 (Hoskin *et al*. 2007), respectively. In both scenarios, it can be seen that biochemical relapse-free survival is improved in patients treated with EBRT in combination with HDR brachytherapy compared to those treated with EBRT alone. However, this improvement is noticeably larger in Sathya *et al*. 2005.

Figure 63: Scenario 1 using biochemical relapse-free survival from Sathya *et al*. 2005

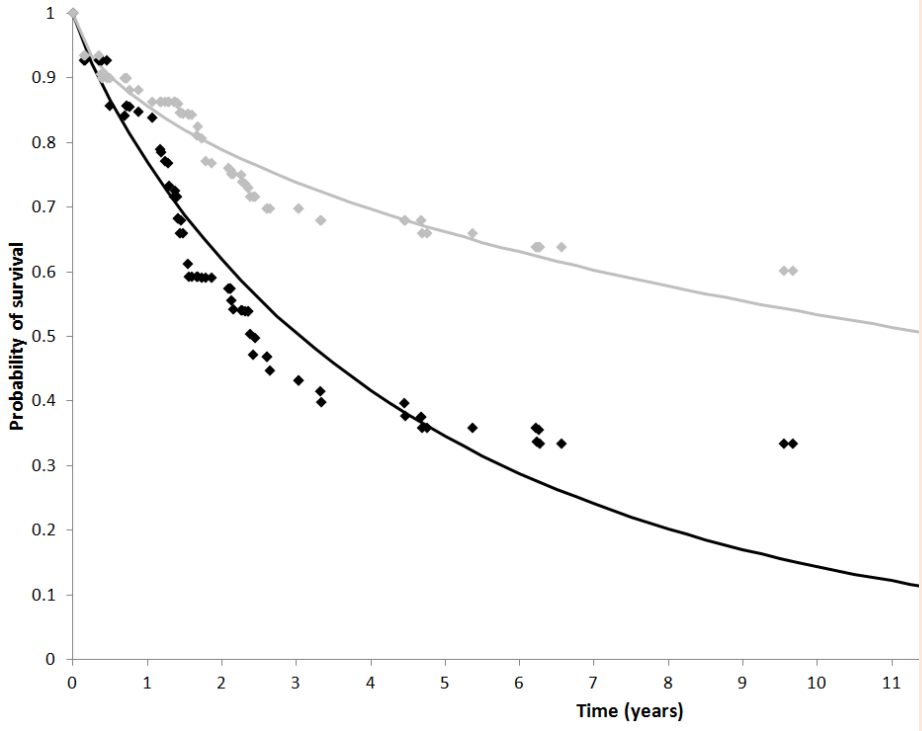
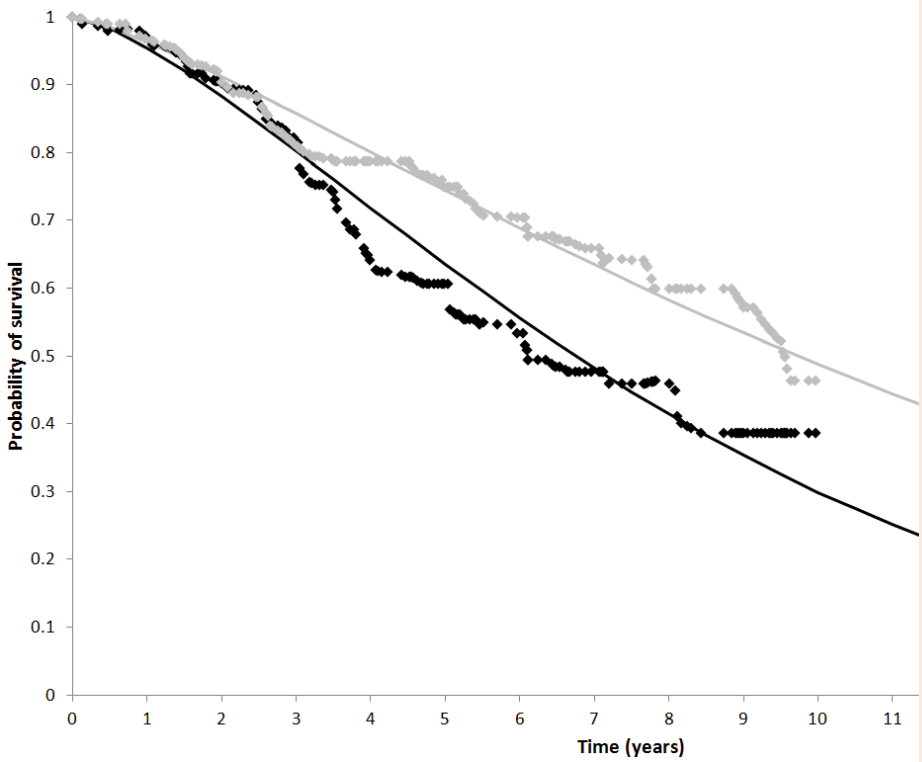


Figure 64: Scenario 2 using biochemical relapse-free survival from Hoskin *et al*. 2007



Update 2014

E.4.12 Treatment-related adverse events

The occurrence of adverse events that patients may experience while receiving treatment was based on the studies identified in the clinical evidence review (Sathya *et al*. 2005 and Hoskin *et al*. 2012). The adverse event probabilities applied in the model are shown in table 97 along with their respective reference.

Table 97: Treatment related adverse event probabilities applied in the model

Treatment related adverse event	Proportion experiencing event		Source
	EBRT	EBRT+HDR-BT	
Sexual dysfunction	67.9%	68.6%	Sathya *et al*. 2005
Urinary incontinence	18.6%	22.2%	Pooled probability from Sathya *et al*. 2005 and Hoskin *et al*. 2012
Bowel dysfunction	4.3%	6.3%	Pooled probability from Sathya *et al*. 2005 and Hoskin *et al*. 2012

E.5 Cost data

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. All costs were estimated in 2011-12 prices.

The majority of costs were sourced from NHS reference costs 2011/12 by applying tariffs associated with the appropriate HRG code . Drug costs were calculated using dose and unit cost information from the British National Formulary (BNF), resource use and cost information from the Personal Social Services Research Unit (PSSRU).

Update 2014

E.5.1 Radiotherapy treatment costs

The radiotherapy costs applied in the EBRT alone arm and EBRT plus HDR brachytherapy arm are shown in tables 98 and 99 below for scenario 1 (Sathya *et al*. 2005) and scenario 2 (Hoskin *et al*. 2007/12), respectively. Costs are calculated using doses and fractions reported in the trials combined with the appropriate costs from the NHS reference cost 2011/127. EBRT was assumed to be an outpatient procedure while HDR brachytherapy was assumed to be an inpatient procedure in scenario 1 (Sathya *et al*. report that HDR brachytherapy was delivered over 48 hours) and as a 'daycase plus regular day/night' in scenario 2 (Hoskin *et al*. report that HDR brachytherapy was delivered over 24 hours).

Costs are separated into 'one-off' costs, which are typically associated with the treatment or procedure itself and 'on treatment' costs, which patients receive for the duration of their treatment.

Table 98: Treatment strategy related costs applied in scenario 1 of the economic model (doses based on Sathya *et al*. 2005)

Treatment strategy and itemised costs	Cost
EBRT alone – Sathya *et al*. 2005	
'One-off' costs:	
EBRT Planning	£819.27 (NHS Reference costs 2011-12)
EBRT delivery cost (66 Gy in 33 fractions)	£3,909.51 (NHS Reference costs 2011-12)

Urology follow-up	£128.91 (NHS Reference costs 2011-12)
Total one-off costs	**£4,857.69**
'On treatment' costs:	
Hormone cost (leuproprelin) given continuously or intermittently	£870.86 (Joint Formulary Committee)
EBRT + HDR brachytherapy – Sathya *et al*. 2005	
'One-off' cost:	
EBRT Planning	£819.27 (NHS Reference costs 2011-12)
EBRT delivery cost (40 Gy in 20 fractions)	£2,369.40 (NHS Reference costs 2011-12)
HDR brachytherapy planning	£1,312.10 (NHS Reference costs 2011-12)
HDR brachytherapy delivery cost (30 Gy in 1 dose over 48 hours)	£2,830.00 (NHS Reference costs 2011-12)
Urology follow-up	£128.91 (NHS Reference costs 2011-12)
Total one-off costs	**£7,459.68**
'On treatment' costs:	
Annual cost of LHRHa (Leuproprelin) given continuously or intermittently	£870.86 (Joint Formulary Committee)

Update 2014

Table 99: Treatment strategy related costs applied in scenario 2 of the economic model (doses based on Hoskin *et al*. 2007/12)

Treatment strategy and itemised costs	Cost
EBRT alone – Hoskin *et al*. 2007/12	
'One-off' costs:	
EBRT Planning	£819.27 (NHS Reference costs 2011-12)
EBRT delivery cost (55 Gy in 20 fractions)	£2,369.40 (NHS Reference costs 2011-12)
Urology follow-up	£128.91 (NHS Reference costs 2011-12)
Total one-off costs	**£3,317.58**
'On treatment' costs:	
Annual cost of LHRHa (Leuproprelin) given continuously or intermittently	£870.86 (Joint Formulary Committee)
EBRT + HDR brachytherapy – Hoskin *et al*. 2007/12	
'One-off' cost:	
EBRT Planning	£819.27 (NHS Reference costs 2011-12)
EBRT delivery cost (35.75 Gy in 20 fractions)	£1,540.11 (NHS Reference costs 2011-12)
HDR brachytherapy planning	£933.42 (NHS Reference costs 2011-12)
HDR brachytherapy delivery cost (17 Gy in 2 fractions over 24 hours)	£1,382.88 (NHS Reference costs 2011-12)
Urology follow-up	£128.91 (NHS Reference costs 2011-12)
Total one-off costs	**£4,804.59**
'On treatment' costs:	
Annual cost of LHRHa (Leuproprelin) given continuously or intermittently	£870.86 (Joint Formulary Committee)

Update 2014

E.5.2 Metastatic treatment costs

The costs associated with treatment strategies that metastatic patients may receive are shown in table 100. The costs were based on the methodology used in the LSHTM model report but with costs updated to reflect the 2011/12 price year. Costs are separated into 'one-off' costs, which are typically associated with the treatment or procedure itself and 'on treatment' costs, which patients receive for the duration of their treatment.

Table 100: Metastatic treatment strategy costs applied in the model

Treatment strategy and itemised costs	Cost
First line: Continuous hormones	
'One-off' cost	
Urology follow-up	£128.91 (NHS Reference costs 2011-12)
'On treatment' costs	
Annual cost of LHRHa (Leuproprelin) given continuously	£902.88 (Joint Formulary Committee)

First line: Intermittent hormones	
'One-off' cost	
Urology follow-up	£128.91 (NHS Reference costs 2011-12)
'On treatment' costs	
Annual cost of LHRHa (Leuproprelin) given intermittently	£601.92 (Joint Formulary Committee)
Second line: LHRHa+bicalutamide	
'One-off' cost	
Urology follow-up	£126.33 (NHS Reference costs 2011-12)
'On treatment' costs	
Bicalutamide 50mg	£57.27 (Joint Formulary Committee)
Annual cost of LHRHa (Leuproprelin) given continuously	£902.88 (Joint Formulary Committee)
Third line: Dexamethasone	
'One-off' cost	
Urology follow-up	£122.46 (NHS Reference costs 2011-12)
'On treatment' costs	
Dexamethasone annual cost	£1,982.79 (Joint Formulary Committee)
Fourth line (chemotherapy)	
Docetaxel+prednisolone	
'One-off' cost	
First clinical oncologist	£159.42 (NHS Reference costs 2011-12)
Admin complex chemotherapy (1st)	£248.29 (NHS Reference costs 2011-12)
'On treatment' costs	
Admin susbequent chemotherapy	£283.89 (NHS Reference costs 2011-12)
Docetaxel three weekly cost	£1,023.00 (Joint Formulary Committee)
Prednisolone three weekly cost	£14.79 (Joint Formulary Committee)
Mitoxantrone+prednisolone	
'One-off' cost	
First clinical oncologist	£159.42 (NHS Reference costs 2011-12)
Admin complex chemotherapy (1st)	£248.29 (NHS Reference costs 2011-12)
'On treatment' costs	
Admin susbequent chemotherapy	£283.89 (NHS Reference costs 2011-12)
Mitoxantrone three weekly cost	£100.00 (Joint Formulary Committee)
Prednisolone three weekly cost	£14.79 (Joint Formulary Committee)

Update 2014

Prednisolone	
'One-off' cost	
First clinical oncologist	£159.42 (NHS Reference costs 2011-12)
'On treatment' costs	
Prednisolone three weekly cost	£14.79 (Joint Formulary Committee)

E.5.3 Radical treatment related adverse event costs

The costs associated with the adverse events that patients may experience while receiving radical treatment are shown in table 101 along with their reference. The costs associated with sexual dysfunction are based on the cost of specialist erectile dysfunction services from NHS reference costs 2011-2012. The costs associated with urinary incontinence were based on the assumption that patients will be continuously managed using containment pads with costs sourced from a recent HTA by Ramsay *et al*. 2012. The costs associated with bowel dysfunction were based on the methodology employed in a recent HTA by Hummel *et al*. 2012, with costs updated to reflect the price year considered in the analysis.

Table 101: Adverse event related costs applied in the model

Adverse events	Proportion	Source
Sexual dysfunction		
Specialist erectile dysfunction services	£151.21	NHS reference costs 2011/12
Urinary incontinence		
Managed by containment pads	£263.60	HTA by Ramsay *et al*. 2012
Bowel dysfunction		
Mean weighted cost that incorporates the costs associated with sigmoidoscopy, laser therapy, enemas and blood transfusion†	£1,687.65	HTA by Hummel *et al*. 2010 and NHS reference costs 2011/12

† Uses proportions of patients with Grade 2 and Grade 3 bowel dysfunction reported in a recent HTA by Hummel et al. 201011

E.5.4 Other costs

Other costs associated with the management and monitoring of prostate cancer patients are captured as the model progresses. These costs are shown in table 102. The costs were obtained from the NHS reference costs 2011-127 by applying the relevant HRG code.

Update 2014

Table 102: Other costs applied in the model

Treatment	Mean unit cost (£)	Source
Urology consultant (1st)	£128.91	NHS reference costs 2011/12 - Urology First attendance non-admitted face to face
Urology consultant (follow up)	£93.96	NHS reference costs 2011/12 - Urology in Follow up attendance non-admitted face to face
Surgical consultant (1st)	£144.98	NHS reference costs 2011/12 - General surgery in First attendance non-admitted face to face
Surgical consultant (follow up)	£110.09	NHS reference costs 2011/12 - General surgery in Follow up attendance non-admitted face to face
Clinical oncology consultant (1st)	£159.42	NHS reference costs 2011/12 - Clinical oncology in First attendance non-admitted face to face
Clinical oncology consultant (follow up)	£113.17	NHS reference costs 2011/12 - Clinical oncology' in 'Follow up attendance non-admitted face to face
Telephone follow up	£47.36	NHS reference costs 2011/12 - Urology in consultant led follow up non face-to-face
PSA test	£19.60	PSA test from Ramsay *et al*. 2012 (£5.91)10, which was sourced from Newcastle upon Tyne Hospitals NHS Foundation Trust. Plus the cost of a consultation with a practice nurse (£13.69) from Unit health and Social care costs.
CT scan	£92.46	NHS reference costs 2011/12 - Computerised Tomography scan, one area, no contrast, 19 years and over (outpatient)
MRI scan	£144.51	NHS reference costs 2011/12 - Magentic resonance imaging scan, one area, no contrast, 19 years and over (outpatient)
Bone scan	£185.51	NHS reference costs 2011/12 - Nuclear medicine, category 2 (outpatient)
Flexible sigmoidoscopy (every 5 years)	174.05	NHS reference costs 2011/12 - Diagnostic flexible sigmoidoscopy 19 years and over (outpatient)

Update 2014

E.6 Health-related quality of life data

The model estimates effectiveness in terms of life years and quality adjusted life years (QALYs). Life years are estimated by adding the time that each patient has spent in pre-defined 'segments' of the model, with each individual patient potentially taking a different path through the model.

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. The utility values chosen for use in the model are consistent with other recent economic evaluations of prostate cancer (Hummel *et al*. 2010 and Mowatt *et al*. 2013). Utility values for undiagnosed and diagnosed localised and locally advanced prostate cancer were sourced from a cohort study of patients undergoing external beam radiotherapy (Korfage *et al*. 2005). It was assumed that patients with locally advanced prostate cancer for more than 52 months would have a utility value associated with that of castrate resistant prostate cancer (CRPC). The utility value associated with metastatic disease was sourced from a sample of 45 to 70 year old males presenting at a primary care medical facility in the US (Volk *et al*. 2004). Table 103 shows the health state utility values applied in the analysis.

Update 2014

Table 103: Health state utilities applied in the model

Health state	Utility	Reference
Localised (undiagnosed)	0.890	Korfage *et al*. 2005
Localised (diagnosed)	0.880	Korfage *et al*. 2005
Locally advanced (undiagnosed)	0.810	Korfage *et al*. 2005
Locally advanced (diagnosed)	0.810	Korfage *et al*. 2005
Castrate resistant prostate cancer	0.760	Korfage *et al*. 2005
Metastases	0.635	Volk *et al*. 2004

It was assumed that there would be no further decrements associated with adverse events. This reflects the population included in the Korfage *et al*. 2005 who had numerous treatment-related morbidities but nonetheless reported high QoL values13.

E.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 65.

Figure 65: Calculation of the incremental cost-effectiveness ratio (ICER)

$$\text{ICER} = (\Delta \text{ Cost}) / (\Delta \text{ QALYs})$$

$$\text{ICER} = (\text{Cost Intervention A} - \text{Cost Intervention B}) / (\text{QALYs Intervention A} - \text{QALYs Intervention B})$$

Update 2014

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 willingness to pay (WTP) 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.

E.7.1 Model results

The results of the model when running scenarios 1 and 2 are shown in the relevant sections below. It should be noted that as the results represent the full prostate cancer treatment pathway, the absolute values should be interpreted with caution. That is, in this scenario, the results do not only reflect the costs and benefits associated with the interventions under consideration (EBRT and EBRT in combination with HDR brachytherapy). Indeed, some patients in the model would not have even received these interventions. However, importantly, the incremental results can be interpreted in the usual way.

Note that one-way sensitivity analysis and probabilistic sensitivity analysis has not been conducted for this analysis. This is because the topic was not originally intended to be modelled and as such modelling priorities lie elsewhere. Furthermore, the GDG felt that there were significant limitations with the evidence base in this area and that running further analyses with this data would be of limited use in the decision making process.

E.7.12 Scenario 1 results

The cost-effectiveness results of the model for scenario 1 are presented in tables 104 and 105 for a cohort of 200,000 patients and an individual patient, respectively. It can be seen that, in comparison to EBRT alone, EBRT in combination with HDR brachytherapy increases life years and QALYs (0.07 and 0.11 per patient, respectively) but this comes at an increased cost (£322 per patient). The ICER shows that EBRT in combination with HDR brachytherapy provides one additional QALY at a cost of £2,804. Thus, as this figure is below a commonly accepted willingness to pay threshold of £20,000 per QALY, EBRT in combination with HDR brachytherapy would be considered cost-effective in this scenario.

Table 104: Total expected costs, QALYs and ICER per cohort of 200,000 patients in scenario 1

Outcome	EBRT+HDR brachytherapy	EBRT only	Incremental
Total Costs	£1,714,399,677	£1,649,977,991	£64,421,686
Total Lys	2,011,635	1,997,954	13,680
Total QALYs	1,763,421	1,740,445	22,976
ICER (cost per QALY)			£2,804

Table 105: Total expected costs, QALYs and ICER per individual patient in scenario 1

Outcome	EBRT+HDR brachytherapy	EBRT only	Incremental
Total Costs	£8,572	£8,250	£322
Total Lys	10.06	9.99	0.07
Total QALYs	8.82	8.70	0.11
ICER (cost per QALY)			£2,804

Update 2014

E.7.13 Scenario 2 results

The cost-effectiveness results of the model for scenario 2 are presented in tables 106 and 107 for a cohort of 200,000 patients and an individual patient, respectively. It can be seen that, in comparison to EBRT alone, EBRT in combination with HDR brachytherapy increases life years and QALYs (0.03 and 0.04 per patient, respectively) but this comes at an increased cost (£177 per patient). The ICER shows that EBRT in combination with HDR brachytherapy provides one additional QALY at a cost of £3,931. Thus, as this figure is below a commonly accepted willingness to pay threshold of £20,000 per QALY, EBRT in combination with HDR brachytherapy would be considered cost-effective in this scenario.

Table 106: Total expected costs, QALYs and ICER per cohort of 200,000 patients in scenario 2

Outcome	EBRT+HDR brachytherapy	EBRT only	Incremental
Total Costs	£1,661,049,878	£1,625,695,714	£35,354,164
Total Lys	2,013,362	2,008,092	5,270
Total QALYs	1,764,467	1,755,474	8,993
ICER (cost per QALY)			£3,931

Table 107: Total expected costs, QALYs and ICER per individual patient in scenario 2

Outcome	EBRT+HDR brachytherapy	EBRT only	Incremental
Total Costs	£8,305	£8,128	£177
Total Lys	10.07	10.04	0.03
Total QALYs	8.82	8.78	0.04
ICER (cost per QALY)			£3,931

E.8 Discussion and conclusions

This analysis aimed to estimate the cost-effectiveness of brachytherapy in combination with EBRT in comparison to EBRT alone. It was not possible to model a strategy of LDR brachytherapy in combination with EBRT because of a lack of high quality evidence in this area. However it was possible to model a comparison of HDR brachytherapy in combination with EBRT versus EBRT alone using the results of two RCTs. The results suggest that, in comparison to EBRT alone, HDR brachytherapy in combination with EBRT is cost-effective in both scenarios modelled, providing one additional QALY at a cost of £2,804 and £3,931 in scenario 1 and scenario 2, respectively.

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 analysis, the effectiveness estimates were drawn from RCTs, which generally represent the best standard of evidence available. However, the doses used in the EBRT only arms of these trials (66 Gy and 50 Gy in Sathya *et al*. 20052 and Hoskin *et al*. 2007/125,6, respectively) were below the minimum standard of 74 Gy recommended in the 2008 NICE prostate cancer guideline. This hinders the applicability of the evidence to current practice.

Furthermore, in the RCT by Sathya *et al*. 20052, the overall dose given in the EBRT arms was inferior to the overall doses given in the EBRT in combination with HDR brachytherapy arm. Thus, it is unclear how much of the improved effectiveness observed in the intervention arm can be attributed to the method used (i.e. brachytherapy) rather than the increased dose.

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 particular issue with the present economic evaluation is the extent to which adverse events are incorporated in quality of life estimates. It was assumed that the impact of adverse events is already incorporated in the quality of life estimates because numerous patients within the study were suffering from adverse events. However, the quality of life values within this study were relatively high and so it is possible that the full detrimental impact of adverse events has not been accurately captured.

In conclusion, the economic analysis suggests that HDR brachytherapy in combination with EBRT is a cost-effective use of resources. However, there are concerns about the applicability of the evidence upon which this conclusion is based because of doses used in the RCTs. Further research is required that investigates the cost-effectiveness of the strategies when using doses that would be typical of clinical practice and considers equivalent overall doses in both arms.

Update 2014

E.9 References

Curtis, L. Unit Costs of Health and Social Care 2012, Personal Social Services Research Unit (PSSRU), University of Kent, Canterbury (2010).

Hoskin, P. J., Motohashi, K., Bownes, P., Bryant, L. & Ostler, P. (2007) High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology, 84: 114-120.

Hoskin, P. J., Rojas, A. M., Bownes, P. J., Lowe, G. J., Ostler, P. J. & Bryant, L. (2012) Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiotherapy & Oncology, 103: 217-222.

Hummel S, Simpson E, Hemingway P, Stevenson MD, Rees A. Intensity-modulated radiotherapy for the treatment of prostate cancer: A systematic review and economic evaluation. Health Technol Assess 2010;14:1-133.

Joint Formulary Committee. British National Formulary (online ed. 65) London: BMJ Group and Pharmaceutical Press <http://www.bnf.org>

Korfage IJ, Essink-Bot ML, Borsboom GJ, Madalinska JB, Kirkels WJ, Habbema JD *et al*. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Int J Cancer 2005;116:291-6.

Lord J, Willis S, Eatock J, Tappenden P, Trapero-Bertran M, Miners A, Crossan C, Westby M, Anagnostou A, Taylor S, Mavranezouli I, Wonderling D, Alderson P, Ruiz F. Economic modelling of diagnostic and treatment pathways in NICE clinical guidelines: the MAPGuide project. Under review

Mowatt G, Scotland G, Boachie C, Cruickshank M, Ford JA, Fraser C, Kurban L, Lam TB, Padhani AR, Royle J, Scheenen TW, Tassie E. Systematic review of the diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, 2013.

NHS reference costs 2011-12 [database on the Internet]. London: UK Department of Health; [accessed March 2013].

Ramsay C, Pickard R, Robertson C, Close A, Vale L, Armstrong N *et al*. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery for removal of the prostate in men with localised prostate cancer. Health Technol Assess 2012

Sathya, J. R., Davis, I. R., Julian, J. A., Guo, Q., Daya, D., Dayes, I. S., Lukka, H. R. & Levine, M. (2005) Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 23: 1192-1199.

Sylvester JE, Grimm PD, Blasko JC, Millar J, Orio PF, Skoglund S *et al*. 15-Year biochemical relapse free survival in clinical Stage T1-T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. International Journal of Radiation Oncology* Biology* Physics 2007; 67(1):57-64.

Volk RJ, Cantor SB, Cass AR, Spann SJ, Weller SC, Krahn MD. Preferences of husbands and wives for outcomes of prostate cancer screening and treatment. J Gen Intern Med 2004;19:339-48.

Widmark A, Klepp O, Solberg A, Damber JE, Angelsen A, Fransson P *et al*. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 2009; 2008/12/19:301-308.

Appendix F:Abbreviations

ACTH	Adrenocorticotropic hormone
ADT	Androgen deprivation therpay
AGSC	Atypical glands suspicious for carcinoma
AS	Active surveillance
ASAP	Atypical small acinar proliferation
ASR	Age standardised ratio
BMD	Bone mineral density
BPH	Benign prostatic hyperplasia
BRCA 1+2	Breast cancer susceptibility gene 1 and 2
BAUS	British Association of Urological Surgeons
CAB	Combined androgen blockade
CT	Computed tomography
DCE MRI	Dynamic contrast enhanced magnetic resonance imaging
DH	Department of Health
DRE	Digital rectal examination
DW MRI	Diffusion weighted magnetic resonance imaging
DXT	Deep x-ray therapy
EBRT	External beam radiotherapy
ED	Erectile dysfunction
ftPSA	Free-to-total prostate specific antigen
GDG	Guideline development group
GI	Gastrointestinal
GRADE	Grading of recommendations, assessment, development and evaluation
GU	Genitourinary
HDR-BT	High-dose rate brchytherapy
HES	Hospital episode statistics
HGPIN	High-grade prostatic intraepithelial neoplasia
HIFU	High intensity focused ultrasound
HR	Hazard ratio
HRPC	Hormone relapsed prostate cancer
HRQoL	Health related quality of life
HSCIC	Health and social care information centre
HT	Hormone therapy
ICER	Incremental cost effectiveness ratio
IMRT	Intensity modulated radiotherapy
LHRHa	Luteinising hormone-releasing hormone agonists
LDR-BT	Low-dose rate brachytherapy
LP	Laparoscopic prostatectomy
LUTS	Lower urinary tract symptoms
MDT	Multi-disciplinary team
mp MRI	Multi-parametric magnetic resonance imaging
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy

NATCANSAT	National Cancer Services Analysis Team
NCC-C	National Collaborating Centre for Cancer
NCIN	National Cancer Intelligence Network
NICE	National Institute for Health and Clinical Excellence
ONS	Office for National Statistics
OP	Open prostatectomy
OR	Odds ratio
PCA3	Prostate cancer antigen 3
PCRMP	Prostate Cancer Risk Management Programme
PDE5	Phosphodiesterase type 5
PEDW	Patient episode database Wales
PET	Positron emission tomography
PME	Pelvic floor muscle exercise
PSA	Prostate specific antigen
PSAd	Prostate specific antigen density
PSAdt	Prostate specific antigen doubling time
PSAv	Prostate specific antigen velocity
QALY	Quality adjusted life years
RALP	Robot assisted laparoscopic prostatectomy
RCT	Randomised controlled trial
RIE	Radiation-induced enteropathy
RP	Radical prostatectomy
RR	Realative risk
RRP	Retropubic radical prostatectomy
RT	Radiotherapy
Sr-89	Strontium 89
SRE	Skeletal related event
SWPHO	South West Public Health Observatory
TRUS	Trans-rectal ultrasound
TURP	Trans-urethral resection of the prostate
WCISU	Welsh Cancer Intelligence and Surveillance Unit
WW	Watchful waiting

1

Appendix G: Glossary

Active surveillance Update 2014

This is part of a 'curative' strategy and is aimed at men with localised prostate cancer who are suitable for radical treatments, keeping them within a "window of curability" whereby only those whose tumours are showing signs of progressing, or those with a preference for intervention are considered for radical treatment. Active surveillance may thus avoid or delay the need for radiation or surgery.

Adjuvant treatment

A treatment given during and after the main treatment.

Androgens

A family of hormones that promote the development and maintenance of male sex characteristics.

Androgen deprivation

A treatment that lowers testosterone levels, that is, bilateral orchidectomy or treatment with LHRH agonists (e.g. goserelin).

Androgen blockade

The use of drugs that bind to and block the hormone receptors of cancer cells, preventing androgens from stimulating cancer growth.

Anti-androgen drugs

Drugs that act by binding to and blocking the hormone receptors of cancer cells, thereby preventing androgens from stimulating the cancer (e.g. bicalutamide).

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.

Benign

Something that does not metastasise and treatment or removal is curative.

Benign Prostatic Hyperplasia (BPH)

A non-cancerous condition in which an overgrowth of prostate tissue pushes against the urethra in some men, restricting the flow of urine. Also known as benign prostatic hypertrophy.

Biochemical free survival Update 2014

The state of being alive and well after radical treatment with no evidence of recurrence as defined by PSA.

Biopsy

Removal of a sample of tissue from the body to assist in diagnosis of a disease.

Bisphosphonates

Update 2014

Calcium-regulated drugs which inhibit bone resorption, used in the treatment of hypercalcemia, osteoporosis and bone pain.

Bowel toxicity

Symptoms caused by treatment-related damage to the bowel.

Brachytherapy

A form of radiotherapy in which the radiation is given using either permanently implanted radioactive seeds (low dose rate) or temporarily inserted radioactive sources (high dose rate) directly into the prostate.

Cancer networks

A cancer network brings together all organisations involved in planning, commissioning and delivery of cancer services in order to provide high quality care across their locality. Typically a cancer network services a population of around one or two million people. Cancer Networks became part of Strategic Clinical Networks, serving larger populations, in April 2013.

Clinically detected disease

Cancer that came to light as a result of a symptom or abnormal clinical finding.

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.

Combined androgen blockade (CAB) / Maximum androgen blockade (MAB)

Update 2014

The combined use of LHRHa's and anti-androgen treatment.

Comorbidity

The effect of all other diseases an individual patient might have other than the primary disease of interest.

Computed tomography (CT)

Imaging technique in which the patient 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.

Counselling

Counselling takes place when a counsellor sees a client in a confidential setting to explore a difficulty the client is having, distress they may be experiencing or their dissatisfaction with life.

Cryotherapy

A treatment which aims to eradicate prostate cancer by freezing the prostate gland.

Decision aids

Booklets or videos/DVDs that provide information about the disease, treatment options and outcomes, and help patients to explore how their individual values impact on their treatment decision.

Digital rectal examination (DRE)

An examination in which a healthcare professional inserts a lubricated, gloved finger into the rectum to feel for abnormalities.

Disease free survival

Length of time after treatment during which no disease is found.

Distant spread

Spread of cancer from the primary site to nearby lymph glands or more distant parts of the body (also known as 'metastatic' or 'secondary' spread).

Endorectal coil imaging

A type of medical imaging in which MRI is used in conjunction with a coil placed into the rectum in order to obtain high quality images of the prostate gland.

Erectile dysfunction

A consistent inability to sustain an erection sufficient for sexual intercourse.

External beam radiotherapy (EBRT)

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 patient.

Flexible sigmoidoscopy

The inspection of the rectum and sigmoid colon by the aid of a flexible sigmoidoscope.

Fistulation

Formation of a fistula in a part of the body. A fistula is an abnormal passage between two internal organs or from an internal organ to the body surface.

Free PSA

The level of free PSA (i.e. PSA that is not bound to other proteins) in the blood.

Gleason score

An internationally recognised grading system, based on examination of prostate tissue, where a pathologist allocates an overall cell abnormality score that can help predict prostate tumour behaviour. A low Gleason score (≤6) indicates a relatively favourable cancer, a high Gleason score (≥8) indicates a relatively aggressive cancer.

Grading

The degree of malignancy of a tumour, judged by its appearance under the microscope.

Gynaecomastia

Enlargement of the breasts in men.

Haematoma

A localised collection of blood, usually clotted, in an organ, space or tissue, due to a break in the wall of a blood vessel.

Haematuria

Red blood cells within the urine, classified as visible (previously macroscopic) and non visible (previously microscopic) – suggested by urine strip tests and confirmed by looking at the urine under a microscope.

Haemorrhagic changes

Changes to blood vessels in the lining of the bladder or bowel which makes them more fragile and likely to bleed.

High intensity focused ultrasound (HIFU)

A technique where high-frequency ultrasound waves are aimed at the cancer, heating up the cells with the aim of causing cell death and eradicating the cancer.

Hormonal therapy

Treatment of cancer by removing and/or, blocking the effects of hormones which stimulate the growth of prostate cancer cells.

Hormone relapsed (previously known as hormone resistant, hormone refractory and castrate resistant)

Update 2014

Refers to prostate cancer following failure of primary androgen deprivation therapy.

Hypercalcaemia

A medical condition in which abnormally high concentrations of calcium compounds are found in the bloodstream.

Incidence

The number of new cases of a disease in a given time period.

Isotope bone scan

An imaging technique which uses an injection of a short-lived radio-active isotope to show up abnormal areas of the bone with high cell metabolism, common to cancers or infections.

Karnofsky status

Classifies patients according to their functional impairment.

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.

Locally advanced prostate cancer

Update 2014

For the purposes of this guideline, this includes: high-risk localised prostate cancer (as defined in chapter 4); T3b and T4, N0 prostate cancer; and any T, N1 prostate cancer.

Focal therapy

Treatment that is directed at tumour cells in one localised area.

Localised prostate cancer

Cancer which has been staged as T1 or T2 (confined to the prostate gland).

LHRHa (Luteinising hormone-releasing hormone agonists)

Hormonal drugs that inhibit the production of androgens from the testes.

Lymphadenectomy

A surgical procedure in which lymph nodes are removed for analysis.

Lymphadenopathy

Disease or swelling of the lymph nodes.

Lymph nodes

Small organs which act as filters in the lymphatic system. Lymph nodes close to the primary tumour are often the first sites to which cancer spreads.

Malignant

Cancerous malignant tumours can invade and destroy nearby tissue and spread to other parts of the body.

Magnetic resonance imaging (MRI)

A non-invasive method of imaging using fluctuating high magnetic fields to depict tissues and organs (also known as nuclear magnetic resonance).

Multiparametric MRI

Update 2014

Magnetic Resonance Imaging study that incorporates anatomical and functional information about a body part. The functional information may include one or more sequences based on diffusion weighted imaging, dynamic contrast enhanced imaging or magnetic resonance spectroscopy.

Magnetic resonance spectroscopy imaging (MRS)

A non-invasive imaging method that provides information about cellular activity (metabolic information). It is used in oncology along with magnetic resonance imaging (MRI) which provides information about the shape and size of the tumour (spacial information).

Maximum androgen blockade (MAB) / Combined androgen blockade (CAB)

Update 2014

The combined use of LHRHa's and anti-androgen treatment.

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 the primary site to somewhere else via the bloodstream or the lymphatic system.

Metastatic prostate cancer

Cancer which has spread from the primary site in the prostate to the lymph nodes, bones or other parts of the body.

Morbidity

The state of being diseased.

Mortality

Either (1) the condition of being subject to death; or (2) the death rate, which reflects the num- ber of deaths per unit of population in any specific region, age group, disease or other classifi- cation, usually expressed as deaths per 1,000, 10,000 or 100,000.

Multi Disciplinary Team (MDT)

A team with members from different health care professions (e.g. urology, oncology, pathology, radiology, nursing).

Myelosuppressive chemotherapy

Chemical agents, used to treat malignant tumours that also can inhibit bone marrow activity, resulting in decreased production of white blood cells.

Neoadjuvant

Treatment given before the main treatment.

Nadir

The lowest measured amount.

Nomograms

A calculating device based on statistical probabilities, which is used to provide individualised estimates of the likelihood of clinical outcomes.

Obstructive uropathy

Impairment of kidney function as a result of back pressure caused by obstruction of the urethra or lymph nodes. This may be a result of prostatic or lymph nodal disease.

Oncology

The study of cancers.

Orchidectomy (also known as bilateral subcapsular orchidectomy)

Surgery to remove the active component of both testicles in order to reduce the level of testosterone.

Osteoporosis

Loss of bony tissue resulting in bones that are brittle and liable to fracture.

PDE5 inhibitor

A drug used in the treatment of erectile dysfunction.

Palliative

Anything which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it.

Percutaneous 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.

Perineal prostatectomy

A technique where the prostate is removed through an incision made between the scrotum and the anus.

Plain radiographs

Single X-ray images.

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 how far it has spread and to investigate response to treatment.

Progestogens

A female sex hormone which can either be naturally occurring or synthetic.

Progressive disease

Prostate cancer that shows either clinical, radiological or biochemical evidence of growth.

Prostate

A gland of the male reproductive system which produces fluid for semen.

Prostate biopsies

Removal of samples of tissue from the prostate gland for microscopic examination and other tests.

Prostatectomy

Surgery to remove part, or all of the prostate gland. Radical prostatectomy aims at the removal of the entire prostate gland and lymph nodes. This can be performed by an open approach or by keyhole technique (laparoscopic or robotically assisted laparoscopic prostatectomy).

Prostate intraepithelial neoplasia

An abnormality of prostate tissue identified by microscopic examination. It represents a potentially pre-malignant lesion but may also co-exist with cancer in a small proportion of men.

Prostate Specific Antigen (PSA)

A protein produced by the prostate gland and identified in the blood. Men with prostate cancer tend to have higher levels of PSA in their blood (although most men with prostate cancer have normal PSA levels). PSA levels may also be increased by conditions other than cancer and levels tend to increase naturally with age.

PSA density

The PSA level in the blood relative to the volume of the prostate.

PSA doubling time

Time taken for the PSA level to double.

Update 2014

PSA test

A test which measures PSA levels in the blood.

PSA velocity

The rate of change of PSA level over time.

Radiation induced enteropathy

Gastrointestinal problems arising a result of radiation treatment. Although both acute and late side effects may occur, this usually refers to chronic problems such as bleeding, stricture, ulceration, flatulence, pain and change in bowel habit

Update 2014

Radical treatment

Treatment given with the aim of cure, rather than just improving symptoms.

Radiotherapy

The use of radiation, usually x-rays or gamma rays, to kill tumour cells. This can either be EBRT or brachytherapy.

Randomised controlled trials (RCTs)

A type of experiment which is used to compare the effectiveness of different treatments. The crucial feature of this form of trial is that patients 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.

Resistance exercise Update 2014

Repetitions of sets of exercises designed to increase muscle strength, endurance or size.

Retropubic prostatectomy

A technique where the prostate is removed through an incision in the abdomen.

Salvage local therapy

Local treatment (e.g. radiotherapy, surgery or chryotherapy) given with curative intent for local recurrence following primary radical surgery.

Salvage therapy

Treatment that is given after prostate cancer has progressed, following other treatments.

Salvage radiotherapy

Radiotherapy given with curative intent when disease has reoccurred after surgery.

Sclerotic bone metastases

Secondary cancer deposits in the bone which show on X-rays as areas of increased bone density.

Screen-detected cancer

Cancer identified by screening a defined population (e.g. using PSA measurement).

Staging/TNM staging

Clinical description of the size and extent of a patient's tumour, by allocation into internationally agreed categories.

Survival

Survival is the probability of surviving with a 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 tumour cells throughout the body rather than targeting one specific area.

Telangiectasia

Permanent dilation of groups of superficial capillaries and venules.

Total PSA

The level of PSA in the blood.

Transrectal ultrasound (TRUS)

An ultrasound examination of the prostate using a probe inserted into the rectum.

Trans-urethral resection of the prostate (TURP)

Surgery to remove tissue from the prostate using an instrument inserted via the urethra. Can be used to improve symptoms in men with restriction to their urinary stream from BPH or a prostate tumour.

Ultrasound-guided prostate biopsy

A technique to allow targeted sampling of prostate tissue using a needle guided by images obtained from an ultrasound.

Uraemia

An excess in the blood of urea, creatinine and other nitrogenous end products of protein and amino acids metabolism.

Ureters

The tubes carrying urine from the kidneys to the bladder.

Urethra

The tube leading from the bladder through which urine leaves the body.

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.

Watchful waiting

This is part of a 'controlling' strategy, and is aimed at men with localised prostate cancer who are either not suitable for, or do not ever wish to receive, curative treatment, and instead involves the deferred use of hormone therapy. Accordingly WW avoids the use of surgery or radiation, but implies that curative treatment will not be available; men on WW who require treatment would receive long-term hormone therapy to control their cancer. A significant number of men on WW follow up need no treatment at all during the rest of their lives.

Update 2014

Appendix H: Guideline scope

H.1 Guideline scope 2014

H.1.1 Guideline title

Prostate cancer: diagnosis and treatment

H.1.2 Short title

Prostate cancer

H.1.3 Introduction

H.1.3.1 Clinical guidelines

Clinical guidelines are recommendations by NICE on the appropriate treatment and care of people with specific diseases and conditions within the NHS. They are based on the best available evidence.

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider.

This is an update of 'Prostate cancer: diagnosis and treatment', NICE clinical guideline 58 (2008). See section H.1.10.1 for details of which sections will be updated. We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation.

This update is being undertaken as part of the guideline review cycle.

Update 2014

H.1.3.2 Quality standards

Quality standards are a set of specific, concise quality statements and measures that act as markers of high-quality, cost-effective patient care, covering the treatment and prevention of different diseases and conditions.

For this clinical guideline a NICE quality standard will be produced during the guideline development process, after the development of the clinical guideline recommendations.

This scope defines the areas of care for which specific quality statements and measures will (and will not) be developed.

The guideline and quality standard development processes are described in detail on the NICE website (see H.1.12).

H.1.4 Need for guidance

H.1.4.1 Epidemiology

Cancer research UK statistics suggest that:

- Prostate cancer is the most common cancer in men and makes up 24% of cancer diagnoses in men in the UK.
- Prostate cancer is predominantly a disease of older men but around 25% of cases occur in men younger than 65 years.

- The incidence and mortality rate of prostate cancer is higher in men of black African-Caribbean family origin compared white Caucasian men.
- In 2008, 34,335 men were diagnosed with prostate cancer and there were 9376 deaths from prostate cancer in England, Wales and Northern Ireland.

H.1.4 Current practice

- Most prostate cancer is diagnosed following a blood test in primary care showing elevated prostate-specific antigen (PSA) levels.
- Presentation with metastatic disease is much less common than it was in the 1980s, before the introduction of PSA testing. At diagnosis most prostate cancers are either localised or locally advanced with no evidence of spread beyond the pelvis.
- A number of treatments are available for localised disease, including active surveillance, radical prostatectomy, radical radiotherapy and brachytherapy.
- Hormonal therapy (testosterone suppression) is being used increasingly for men with locally advanced non-metastatic disease.
- A number of new treatments have been licensed for the management of castrate-resistant metastatic prostate cancer[mm] since the publication of NICE clinical guideline 58 (2008).

H.1.5 Clinical guideline

H.1.6 Population

Groups that will be covered

- Men referred from primary care for investigation of possible prostate cancer, in line with 'Referral guidelinesfor suspected cancer' (NICE clinical guideline 27).
- Men with a biopsy-proven diagnosis of primary adenocarcinoma of the prostate, or an agreed clinical diagnosis[nn] if biopsy is inappropriate.
- Consideration will be given to men of African-Caribbean family origin.

Groups that will not be covered

- Asymptomatic men with an abnormal PSA level detected in primary care who are not referred for subsequent investigation.
- Men with metastatic disease of different primary origin involving the prostate.
- Men with rare malignant tumours of the prostate, such as small cell carcinoma and rhabdomyosarcoma.

H.1.6 Healthcare settings

All settings in which NHS care is received– excluding population-based and opportunistic screening.

Update 2014

mm Since the 2008 guideline the term hormone-refractory prostate cancer has been replaced with castrate-resistant metastatic prostate cancer by healthcare professionals as it is more clinically accurate. However, due to its negative connotations for men with the disease the alternative terminology 'hormone relapsed prostate cancer' will be proposed at the GDG, as this remains an accurate description and would be acceptable to patient groups.

nn Agreed clinical diagnosis on the basis of, for example, digital rectal examination, high PSA levels and known metastases.

H.1.7 Management

H.1.7.1 Key issues covered by the update

- Optimal diagnostic strategy in patients referred to secondary care with suspected prostate cancer, including:
  - Initial transrectal ultrasoundbiopsy.
  - If initial biopsy is negative, subsequent investigation (including multiparametric magnetic resonance imaging, 3D ultrasound, and template biopsy) or surveillance.
- Magnetic resonance imaging in the staging of prostate cancer.
- Active surveillance including:
  - Eligibility.
  - Protocol.
- The following methods of radical prostatectomy:
  - retropubic
  - transperineal
  - laparoscopic
  - robot-assisted laparoscopic.
- High dose rate brachytherapy in combination with external beam radiotherapy for localised and locally advanced non-metastatic prostate cancer.
- Combination low dose rate brachytherapy and external beam radiotherapy for localised and locally advanced non-metastatic prostate cancer.
- Combinations of hormones plus external beam radiotherapy for localised or locally advanced non-metastatic prostate cancer.
- Intermittent hormone therapy for men receiving long-term hormonal therapy for prostate cancer.
- Interventions for radiation bowel toxicity after radical radiotherapy.
- Identifying and managing late effects of long-term androgen suppression.

Update 2014

H.1.7.2 Key issues covered by NICE clinical guideline 58 for which the evidence will not be reviewed

- Communication and support.
- Imaging other than in H1.7.1.
- Nomograms.
- Watchful waiting.
- Radiotherapy other than covered in H1.7.1.
- High-intensity focused ultrasound and cryotherapy.
- Follow-up.
- Managing adverse effects of treatment, other than covered in H1.7.1.
- Managing relapse after radical treatment.
- Bisphosphonates in the treatment of prostate cancer.
- Adjuvant hormonal therapyafter radical prostatectomy.
- Hormone-refractory prostate cancer.
- Palliative care.

Key issues that will not be covered

- Referral from primary care with suspected prostate cancer (this will be covered by the update to the 'Referral for suspected cancer' guideline).
- Screening for prostate cancer.
- Cabazitaxel and abiraterone for castrate-resistant metastatic prostate cancer (these are the subject of ongoing NICE technology appraisals).

Main outcomes

- Overall survival (at 5 years, 10 years,and median survival).
- Disease-free survival.
- Biochemical disease-free survival.
- Diagnosis-related morbidity.
- Diagnosis-related mortality.
- Treatment-related morbidity.
- Treatment-related mortality.
- Number and severity of adverse events.
- Health-related quality of life.

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 section 7).

Quality standard

Information on the NICE quality standards development process is available on the NICE website, see section 7.

Areas of care

The areas of care of a patient's pathway used to inform the development of the quality statements are set out in section H.1.10. The content of the quality standard statements may change during the process and may differ after consultation with stakeholders.

Areas of care that will be considered

- Patient information and decision-making, for example counselling and pre-treatment decision-making.
- Multidisciplinary team.
- Prostate biopsy methods.
- Imaging.
- Watchful waiting and active surveillance.
- Radical treatment of localised prostate cancer:
  - surgery
  - radiotherapy
  - brachytherapy.

Update 2014

- Radical treatment of locally advanced prostate cancer withcombined hormones and radiotherapy.
- Access to specialist services for complications of treatment, for example, sexual dysfunction, incontinence, bowel problems.
- Management of biochemical failure following radical local treatment.
- Hormonal therapy.
- Management of castrate-resistant metastatic prostate cancer.
- Metastatic spinal cord compression in men with prostate cancer.
- Follow-up after radical treatment for prostate cancer.
- Supportive and palliative care.

Areas of care that will not be considered

- Screening for prostate cancer.
- Referral from primary care with suspected prostate cancer.

H.1.10 Economic aspects

Developers will take into account both clinical and cost effectiveness when prioritising the quality statements to be included in the quality standard. The economic evidence will be considered, and the cost and commissioning impact of implementing the quality standard will be assessed.

H.1 Status

H.1.1 Scope

This is the final scope.

H.1.2 Timings

The development of the guideline recommendations and the quality standard will begin in February 2012.

H.2 Related NICE guidance

H.2.1 NICE guidance that will be incorporated in or updated by the clinical guideline

This guideline will update the following NICE guidance:

- Prostate cancer. NICE clinical guideline 58 (2008).
- This guideline will incorporate the following NICE guidance (subject to review):
- Docetaxel for the treatment of hormone-refractory metastatic prostate cancer. NICE technology appraisal guidance 101 (2006).

H.2.2 Related NICE guidance

Published

- Denosumab for the treatment of therapy-induced bone loss in non-metastatic prostate cancer (terminated appraisal). NICE technology appraisal 194 (2010).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Metastatic spinal cord compression. NICE clinical guideline 75 (2008).

Update 2014

- Intraoperative red blood cell salvage during radical prostatectomy or radical cystectomy. NICE interventional procedure guidance 258 (2008).
- Laparoscopic radical prostatectomy. NICE interventional procedure guidance 193 (2006).
- High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. NICE interventional procedure guidance 174 (2006).
- Cryotherapy as a primary treatment for prostate cancer. NICE interventional procedure guidance 145 (2005).
- Low dose rate brachytherapy for localised prostate cancer. NICE interventional procedure 132 (2005).
- Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005).
- Cryotherapy for recurrent prostate cancer. NICE interventional procedure guidance 119 (2005).
- High-intensity focused ultrasound for prostate cancer. NICE interventional procedure guidance 118 (2005).
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).
- Transperineal electrovaporisation of the prostate. NICE interventional procedure guidance 14 (2003).
- Improving outcomes in urological cancers. NICE cancer service guidance (2002).
- Service user experience in adult mental health. NICE clinical guideline. NICE clinical guideline 136 (2011).

NICE guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Focal therapy using cryoablation for localised stage prostate cancer. NICE interventional procedure guidance. Publication expected Winter 2011/12.
- Prostate cancer –cabazitaxel. NICE technology appraisal. Publication expected February 2012.
- Focal therapy using high-intensity focused ultrasound (HIFU) for localised prostate cancer. NICE interventional procedure guidance. Publication expected Spring 2012.
- Opioids in palliative care. NICE clinical guideline. Publication expected May 2012.
- Prostate cancer (metastatic, castration resistant) –abiraterone (following cytotoxic therapy). NICE technology appraisal. Publication expected May 2012.
- Bone metastases from solid tumours –denosumab. NICE technology appraisal. Publication expected June 2012.
- Prostate cancer (metastatic, castrate-resistant, not treated with chemotherapy) - abiraterone acetate (with prednisolone). NICE technology appraisal. Publication expected July 2013.
- Patient experience in adult NHS services. NICE clinical guideline. Publication date to be confirmed.
- Prostate cancer (hormone refractory) –atrasentan. NICE technology appraisal. Suspended.
- Prostate cancer (prevention) –dutasteride. NICE technology appraisal. Suspended.
- Prostate cancer – intensity modulated radiotherapy. NICE technology guideline. Suspended.

Update 2014

H.1.13 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual
- 'Developing NICE quality standards: interim process guide'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual andwww.nice.org.uk/aboutnice/qualitystandards). Information on the progress of the guideline and quality standards is also available from the NICE website (www.nice.org.uk).

Update 2014

H.2 Guideline scope 2008

H.2.1 Guideline title

Prostate cancer: diagnosis and treatment

H.2.2 Short title

Prostate cancer

H.2.3 Background

The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Cancer to develop a clinical guideline on the diagnosis and treatment of prostate cancer for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government (see section H.2.11). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness and professional consensus.

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

This guideline will support current national initiatives outlined in the NHS Cancer Plan, the Calman Hine Report, the Cameron Report, the Manual for Cancer Services for England and the Wales Cancer Standards. The guideline will also refer to the NICE service guidance documents

'Improving outcomes in urological cancers' and 'Improving supportive and palliative care for adults with cancer' and the clinical guideline documents 'Referral guidelines for suspected cancer' and 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' (in development).

NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

H.2.4 Clinical need for the guideline

Prostate cancer is one of the commonest cancers in men. Each year there are about 27,773 new cases in England and Wales[oo] [pp] and 9161 deaths[qq]. Prostate cancer is predominantly a disease of older men but around 20% of cases occur in men under the age of 65. Over the past 10 to 15 years there have been a number of significant advances in its management but also a number of major controversies, especially about the clinical management of patients with early, non-metastatic disease. These uncertainties clearly cause anxieties for patients and their families. There is evidence of practice variation around the country and of patchy availability of certain treatments and procedures. A clinical guideline will help to address these issues and offer guidance on best practice.

---

oo Office for National Statistics, Cancer Statistics Registrations: Registrations of cancer diagnosed in 2001, England. Series MB1 no. 32. 2004, National Statistics: London

pp Welsh Cancer Intelligence and Surveillance Unit, 2003

qq Office for National Statistics, Mortality Statistics: Cause. England and Wales 2003. TSO: London

H.2.15 The guideline

The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). The guideline development process – an overview for stakeholders, the public and the NHS describes how organisations can become involved in the development of a guideline. Guideline development methods – information for National Collaborating Centres and guideline developers provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this 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 and Welsh Assembly Government (see section H.2.11).

The areas that will be addressed by the guideline are described in the following sections.

H.2.16 Population

Groups that will be covered

- Adults referred from primary care for investigation of possible prostate cancer, in line with the NICE clinical guidelines on referral suspected cancer (NICE Clinical Guideline no. 27).
- Adults with a biopsy-proven diagnosis of primary adenocarcinoma of the prostate or an agreed clinical diagnosis* when biopsy would be inappropriate. (*Agreed clinical diagnosis on the basis of, for example, digital rectal examination, high prostate-specific antigen [PSA] and known metastases.)
- No patient subgroups needing special consideration have been identified.

Groups that will not be covered

- Asymptomatic adults with an abnormal, age-specific PSA level and no biopsy-proven diag- nosis of prostate cancer.
- Patients with metastatic disease of different primary origin involving the prostate.
- Children and adults with rare malignant tumours of the prostate, such as small cell carci- noma and rhabdomyosarcoma.

H.2.17 Healthcare setting

- Primary care – excluding population-based and opportunistic screening.
- Secondary care.
- Tertiary care by specialist urological cancer teams.

H.2.18 Clinical management

- Investigation to establish a histopathological diagnosis.
- Diagnostic investigations for clinical staging.
- Active surveillance of men with localised disease suitable for radical treatment.
- Surgical management including radical prostatectomy, perineal prostatectomy, laparoscopic prostatectomy, high-frequency ultrasound, radiofrequency ablation and cryotherapy.
- Radiotherapy including external beam, brachytherapy (high and low dose rate) and unsealed radioactive sources (strontium-89 and samarium-153).
- Hormonal treatments: neo-adjuvant, adjuvant and palliative; surgical and pharmacological.
- Cytotoxic chemotherapy: neo-adjuvant, adjuvant and palliative.
- Bisphosphonates.

- Novel biological and immunological agents.
- The management of common treatment-related side effects and complications.
- Patient information, support and specific aids for complex decision making.

H.2.9 Status

Scope

This is the final scope.

NICE appraisals in development

- Docetaxel for the treatment of hormone refractory prostate cancer. Expected date of issue July 2006.
- Atrasentan for hormone refractory prostate cancer. Expected date of issue January 2008.

NICE guidance in development

- Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk. Publication date to be confirmed.
- Lower urinary tract symptoms in men. Publication date to be confirmed.

Related published NICE guidance

- National Institute for Health and Clinical Excellence (2005). Referral guidelines for suspected cancer. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/CG027
- National Institute for Clinical Excellence (2002). Improving outcomes in urological cancers. London: National Institute for Clinical Excellence. Available from www.nice.org.uk/csguc
- National Institute for Clinical Excellence (2004). Improving supportive and palliative care for adults with cancer. London: National Institute for Clinical Excellence. Available from www.nice.org.uk/csgsp

Guideline

The development of the guideline recommendations will begin in November 2005.

H.2.10 Further information

Information on the guideline development process is provided in:

- The guideline development process – an overview for stakeholders, the public and the NHS
- Guideline development methods – information for National Collaborating Centres and guideline developers

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesprocess). Information on the progress of the guideline will also be available from the website.

H.2.11 Referral from the Department of Health and Welsh Assembly Government

The Department of Health and Welsh Assembly Government asked the Institute:

'To prepare a guideline for the NHS in England and Wales for the clinical management of prostate cancer, to supplement existing service guidance. The guideline should cover:

- The key diagnosic and staging procedures – excluding screening

- The main treatment modalities including hormonal treatments (covering surgical and chemical castration)
- The role of tumour specific bisphosphonates.

Appendix I: People and organisations involved in production of the guideline

I.1 Members of the 2014 Guideline Development Group

GDG Chair	
Mr Sean Duffy[rr] Dr John Graham[ss]	Chair, Yorkshire Cancer Network Consultant Lead Clinical Oncologist, Taunton and Somerset NHS Trust
GDG Lead Clinician	
Dr Peter Kirkbride	Lead Clinician, Clatterbridge Cancer Centre
Group Members	
Professor David Neal	Professor of Surgical Oncology, University of Cambridge
Professor Peter Hoskin	Consultant Oncologist, Mount Vernon Cancer Centre
Ms Kathleen Nuttall	Director, Lancashire and South Cumbria Cancer Network
Dr Jon Oxley	Consultant in Cellular Pathology, Southmead Hospital
Professor Howard Kynaston	Professor of Urological Surgery, Cardiff University
Dr Jonathan Richenberg	Consultant Uroradiologist, BSUH NHS Trust
Ms Nicola James	Nurse Consultant, Chesterfield Royal Hospital
Mr Brian McGlynn	Nurse Consultant Urology Oncology, The Ayr Hospital, Ayr
Mr Hugh Butcher	Patient/carer member
Dr Sarah Cant	Patient/carer member, Head of Policy & Campaigns, Prostate Cancer UK

Update 2014

rr From February 2012 to March 2013
ss From March 2013 to January 2014

1 **Declarations of Interest**

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Mr Sean Duffy (Chair)	Asked by Roche to give a lecture on 'Commissioning in the new NHS'. No fee will be received.	Personal Non-Pecuniary	Declare and can participate in discussions on all topics as the content is not related to the guideline.
Dr John Graham (Chair)	Principal investigator of OncoGenex OGX-011-12 trial of cabazitaxel plus or minus custirsen as 2nd line chemotherapy in hormone relapsed prostate cancer. Funded by Teva Pharmaceuticals Ltd.	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as chemotherapy is not being investigated by the guideline.
	Principal investigator of 2. Millenium C21005 trial investigating orteronel versus placebo following 1st line chemotherapy with docetaxel for hormone relapsed prostate cancer. Trial is closed to recruitment but in follow-up. Funded by Takeda Pharmaceuticals.	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as orternoel is not being investigated by the guideline.
Professor Peter Hoskin	Chief investigator for a trial investigating brachytherapy +/- external beam radiotherapy, which received funding from Dept of Health and CRUK. Continues to follow those patients up and publish data from the study	Non-Personal Pecuniary, specific	Declare and can participate in discussions on all topics as payment received more than 10 years ago
	Holds a research grant from Varian which pays the salary for a data manager working on HDR boost	Non-Personal Pecuniary, specific	Declare and must withdraw from discussions on all topics on HDR boost (Chair decision that he can be asked questions)
	Department reimbursed for studies on abiraterone by Cougar	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is non-specific (abiraterone not covered by guideline)
	Department reimbursed for studies on alpharadin by Astellas	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is non-specific (alpharadin not covered by guideline)
	Department reimbursed for studies on MDV 3100 by Medivation	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is non-specific (MDV 3100 not covered by guideline)
	Department reimbursed for	Non-Personal	Declare and must withdraw

Update 2014

	studies on Denosumab by Amgen	Pecuniary, specific	from discussions on all topics on denosumab
	Received travel expenses from Astellas Pharmaceuticals to attend BAUS annual meeting in Liverpool	Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics - expenses not beyond reasonably required
	Received travel expenses from Nucletron to present a lecture on brachytherapy at a meeting	Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics - expenses not beyond reasonably required
	Received honorarium and travel expenses from Accuracy to present a lecture on stereotactic radiotherapy in prostate cancer.	Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as stereotactic radiotherapy is not being covered by the guideline
Professor David Neal	Advises International Health Technology on PSA testing to be used in prostate cancer screening for employees of companies providing private healthcare	Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as PSA testing in screening is not being covered by the guideline
	Co-chair of Prostate Cancer Advisory Group	Personal non-pecuniary	Chair decision declare and can participate in discussions on all topics
	Led a bid to carry out audit of prostate cancer management - tender to be put out shortly by HQIP	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics until bid confirmed
Dr Jon Oxley	Holds shareholding in GlaxoSmithKline Plc.	Personal Pecuniary, specific	Declare and must withdraw from discussions on all topics that include dutasteride or erectile dysfunction interventions
	Astra Zeneca, Novartis and GlaxoSmithKline shares held in a fund	Personal Pecuniary, specific	Declare and can participate in discussions on all topics as has no ability to instruct fund manager on the composition of the fund
Prof Howard Kynaston	Received an honorarium from Takeda for a symposium speaker fee at the BAUS Annual Meeting for presentation entitled “Surgery for high risk localised prostate cancer”.	Personal Pecuniary, specific	Declare and must withdraw from discussions on all topics on surgery until June 2012
	Received travel expenses from Ferring Pharmaceuticals to launch the MRC RADICALS trial in Ireland	Personal Pecuniary, specific	Declare and can participate in discussions on all topics - expenses not beyond reasonably required
	Lead (local) investigator (and on TMG) for Prostate Adenocarcinoma: TransCutaneous Hormones	Non-Personal Pecuniary, specific	Chair persons actions: Declare and can participate in discussions on all topics as not funded by health

	trial. (RCT of transcutaneous oestrogen patches versus LHRH analogues in prostate cancer), which is funded by CRUK		industry
	Lead (local) investigator (and on TMG) for Radiotherapy and Androgen Deprivation In Combination After Local Surgery trail, which is funded through MRC	Non-Personal Pecuniary, specific	Chair persons actions: Declare and can participate in discussions on all topics as not funded by health industry
	Lead (local) investigator for a trial looking at PCA-3 and T2-ERG score changes during initiation of ADT with Triptorelin in patients with advanced prostate cancer (TRIPTOCARE), funded by Ipsen Pharma	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as the patient population in this trial (the use of biomarkers in men selected for hormone therapy) is not being looked at in any guideline topics
	Lead (local) investigator for a prospective observational study cohort to assess the rate of castration resistance, disease progression & overall survival in patients participating in the TRIPTOCARE study, funded by Ipsen Pharma	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as the patient population in this trial (the use of biomarkers in men selected for hormone therapy) is not being looked at in any guideline topics
	Lead (local) investigator for a trial evaluating the safety and effects on bone resporption of AZD0530 in patients with prostate cancer or breast cancer with metastatic bone disease, funded by AstraZeneca	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as the intervention in this trial is not being looked at in any guideline topics
	Lead (local) investigator for a trial looking at Intermittent Androgen Deprivation In Patients With Stage D (metastatic) Prostate Cancer, funded by EORTC	Non-Personal Pecuniary, specific	Chair persons actions: Declare and can participate in discussions on all topics as not funded by health industry
	Lead (local) investigator for a multi-centre study of long term hormonal therapy following a six months combined hormone and radiotherapy regime for prostate cancer, funded by EORTC	Non-Personal Pecuniary, specific	Chair persons actions: Declare and can participate in discussions on all topics as not funded by health industry
	Lead (local) investigator for a trial looking at Initial Antiandrogen Monotherapy In Comparison With Watchful Waiting In	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as not funded by health industry and this comparison is not being investigated in

Update 2014

	Asymptomatic T1-3 (any Gleason) NO Or Nx MO Prostate Cancer, funded by EORTC		this guideline
	UK Chief investigator for a trial looking at intermittent versus continuous androgen deprivation therapy using ELIGARDâ 22.5 mg 3-month depot in subjects with relapsing or locally advanced prostate cancer who are responsive to such therapy, funded by Astellas Pharma Europe	Non-Personal Pecuniary, specific	Declare and must withdraw from discussions on all topics comparing intermittent versus continuous hormone therapy
	Lead (local) investigator for a trial looking at Hormone Therapy Plus Radical Radiotherapy Versus Hormone Therapy Alone in Non-Metastatic Prostate Cancer, funded through MRC	Non-Personal Pecuniary, specific	Chair persons actions: Declare and can participate in discussions on all topics as not funded by health industry
	Lead (local) investigator for a trial looking at the Efficacy and Safety of MDV3100 (ASP9785) vs. Bicalutamide in Castrate Men with Metastatic Prostate Cancer, funded by Astellas Pharma Global	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as the intervention in this trial is not being looked at in any guideline topics
	Part of a team bidding to carry out an audit of prostate cancer management (funded by HQIP). Tender was successful (awarded in April 2013 for 5 years).	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics until bid confirmed
	Co-investigator for a trial evaluating the addition of celecoxib to standard treatment of transitional cell carcinoma of the bladder, funded by the institute of cancer research	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is related to bladder cancer
	Lead (local) investigator for the UK Genetic prostate cancer study, funded by the institute of cancer research	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as genetics are not being covered in this guideline
	Co-investigator for a trial comparing hyperthermia plus mitomycin to a second course of bacillus Calmette-Guérin or standard therapy in patients with recurrence of non-muscle invasive bladder cancer following induction or maintenance bacillus Calmette-Guérin	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is related to bladder cancer

Update 2014

	therapy, funded through University College London		
	Lead (local) investigator for a trial looking at the prognostic impact of renal sinus invasion and vascular invasion study protocol in renal cell carcinoma, funded through Cardiff University	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is related to renal cell carcinoma
	Co-investigator for a trial comparing Sorafenib With Placebo In Patients With Resected Primary Renal Cell Carcinoma at High or Intermediate Risk of Relapse, funded through MRC	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is related to renal cell carcinoma
	Lead (local) investigator for trial looking at Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (docetaxel, zoledronic acid, celecoxib or abiraterone), funded through MRC	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as not funded by health industry and the interventions in this trial is not being looked at in any guideline topics
	Lead (local) investigator looking at the collection of urine specimens to study the possible presence of biomarkers of genitourinary cancer using novel enzyme substrates, funded through Cardiff University	Non-Personal Pecuniary, specific	Chair persons actions: Declare and can participate in discussions on all topics as not funded by health industry
	Co-investigator for European Registry Evaluating Management Practices of General Practitioners and Urologists and Pharmacological Treatment Outcomes in Patients with Lower Urinary Tract Symptoms, funded by EAU research foundation	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is related to Benign Prostatic Hyperplasia
	Lead (local) investigator for a trial comparing intermittent versus continuous androgen suppression for patients with PSA progression in the clinical absence of distant metastases following radiotherapy for prostate cancer, funded through National Institute of Canada Clinical Trials Group	Non-Personal Pecuniary, specific	Chair persons actions: Declare and can participate in discussions on all topics as not funded by health industry
	Lead (local) investigator for Pre Recruitment Evaluation - Optimum Therapy In the	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics - as radiotherapy is not being

	Management of Aggressive Local prostate cancer (radiotherapy versus surgery), funded not yet agreed		compared to surgery in this guideline
	Lead (local) investigator for a trial comparing active surveillance, radiotherapy, prostatectomy in screen detected localised prostate cancer (HTA)	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics - as active surveillance, radiotherapy and prostatectomy are not being compared in screen detected prostate cancer in this guideline
	Chief investigator for the prostate tumour arm of a MRC trial on aspirin adjuvant to curative treatment (ADD), which is funded by CRUK and is due to start in 12 months (awaiting confirmation from HTA funding process).	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as not funded by health industry and the intervention in this trial is not being looked at in any guideline topics
Dr Jonathan Richenberg	Moderated at European Congress Radiology on prostate cancer, attendance fee waived by ECR.	Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics - expenses not beyond reasonably required
	His department is likely to be a centre involved in the PROMIS trial (Prostate MRI Imaging Study – looking at the use of multiparametric MRI as a tool in diagnosing prostate cancer), starting in 2013. It is MRC funded, the trial protocol has already been designed and JR's role will be an investigator. There is no financial interest for JR's department or himself (all MRI costs will be recouped by saving on TRUS biopsies). This was classified as non-personal pecuniary, specific.	Personal non-pecuniary	Chair persons actions to declare and can participate in discussions on all topics as research not funded by health industry.
	Advised that he was an author on a paper due to be published in the Journal of Clinical Radiology. The paper documents the findings of a consensus of British radiologists (from nine centres) about the use of MRI in prostate cancer. JR confirmed that the article does promote specific opinions about the use of MRI in prostate cancer. This was classified as personal non-pecuniary.	Personal non-pecuniary	Chair persons action to declare and participate in discussions on all topics as the paper is based on the consensus of a professional group, not that of one individual.

Mr Hugh Butcher	Received payment from Macmillan to act as a co-researcher on 'Evaluation of NCSI User Involvement Model'	Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is not specific
	Co Chair User Partnership Group (UPG) Yorkshire Cancer Network: in this role sits on the YCN Board, Urology NSSG, Recruitment Selection and Support Sub-committee of the UPG, Executive Committee of UPG, & patient Experience Sub Committee of the UPG.	Personal non-pecuniary	Declare and can participate in discussions on all topics - expenses not beyond reasonably required
	Macmillan Cancer Support – Spiritual Support Task Force	Personal non-pecuniary	Declare and can participate in discussions on all topics - expenses not beyond reasonably required
	Service User representative, receiving an honorarium, on Management Advisory Group: Research Project - Nurse led/primary-care follow up support for prostate cancer survivors, Oxford Brooks University	Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is non-specific (follow-up care is not covered by guideline)
	Member, National User Steering Group for Peer Review	Personal non-pecuniary	Declare and can participate in discussions on all topics - expenses not beyond reasonably required
	Service User Member, NCAT MDT Development Steering Group	Personal non-pecuniary	Declare and can participate in discussions on all topics - expenses not beyond reasonably required
	Deputy Chair, York and District Cancer Partnership Group, York District Hospital	Personal non-pecuniary	Declare and can participate in discussions on all topics - expenses not beyond reasonably required
Dr Sarah Cant	Employed by Prostate Cancer UK which receives sponsorship from Astellas Pharma Europe Ltd., AstraZeneca UK Ltd, GlaxoSmithKline UK Ltd, Ipsen Ltd, Janssen, Novartis Pharmaceuticals UK Ltd. Sanofi-Aventis, Takeda UK Ltd.	Non-Personal Pecuniary, non-specific	Declare and can participate in discussions on all topics as interest is non-specific
	Partner works for Sanofi Pasteur (no shares received in benefit)	Personal family interest	Declare and can participate in discussions on all topics as interest is non-specific
Dr Peter Kirkbride	No declarations received		
Ms Kathleen Nuttall	No declarations received		
Ms Nicola James	No declarations received		

Mr Brain McGlynn	No declarations received		

1

Update 2014

I.2 Organisations invited to comment on the 2014 guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

AAH Pharmaceuticals	Bedfordshire Primary Care Trust
Abbott GmbH & Co KG	Betsi Cadwaladr University Health Board
AbbVie	Birmingham & Brunel Consortium
Abertawe Bro Morgannwg University Health Board	BME Cancer Communities
Advanced Medical Diagnostics	Boehringer Ingelheim
Afiya Trust	Bostwick Laboratories
African Health Policy Network	Bradford District Care Trust
Age UK	Breast Cancer UK
Aintree University Hospital NHS Foundation Trust	Bristol and Avon Chinese Women's Group
Airedale NHS Trust	Bristol Cancer Help Centre
Albyn Medical Ltd	Bristol-Myers Squibb Pharmaceuticals Ltd
Allergan Ltd UK	Bristol-Myers Squibb Pharmaceuticals Ltd
Allocate Software PLC	British Association for Cytopathology
Almac Diagnostics	British Association of Art Therapists
American Medical Systems Inc.	British Association of Urological Nurses
Amgen UK	British Association of Urological Surgeons
Aneurin Bevan Health Board	British Dietetic Association
APOGEPHA Arzneimittel GmbH	British Geriatrics Society
Arden Cancer Network	British Lymphology Society
Arrowe Park Hospital	British Medical Association
Arthritis Research UK	British Medical Journal
Ashford and St Peter's Hospitals NHS Trust	British National Formulary
Association for Continence Advice	British Nuclear Cardiology Society
Association for Family Therapy and Systemic Practice in the UK	British Nuclear Medicine Society
Association of Anaesthetists of Great Britain and Ireland	British Pain Society
Association of British Insurers	British Prostate Group
Association of Chartered Physiotherapists in Oncology and Palliative Care	British Psychological Society
Association of Chartered Physiotherapists in Women's Health	British Society for Immunology
Association of Clinical Pathologists	British Society of Interventional Radiology
Astellas Pharma Ltd	British Uro-Oncology Group
Astrazeneca UK Ltd	BUPA Foundation
B. Braun Medical Ltd	C. R. Bard, Inc.
Bard Limited	Calderdale Primary Care Trust
Barnsley Primary Care Trust	Calderstones Partnerships NHS Foundation Trust
Baxter Healthcare	Cambridge University Hospitals NHS

	Foundation Trust
Bayer HealthCare	Camden Link
Cancer Network Pharmacists Forum	Faculty of Public Health
Cancer Network User Partnership	FBA and Brook
Cancer Phytotherapy Service	Ferring Pharmaceuticals
Cancer Research UK	Five Boroughs Partnership NHS Trust
Cancer Services Co-ordinating Group	Fresenius Kabi Ltd
Cancer Voices	Galil Medical
Capsulation PPS	General Practice and Primary Care
Care Quality Commission (CQC)	Genetic Alliance UK
Cariad Technologies Ltd	George Eliot Hospital NHS Trust
Celgene UK Ltd	GlaxoSmithKline
Central & North West London NHS Foundation Trust	Gloucestershire Hospitals NHS Foundation Trust
Central South Coast Cancer Network	Gloucestershire LINk
Chartered Physiotherapists Promoting Continence	Great Western Hospitals NHS Foundation Trust
Chartered Society of Physiotherapy	Greater Manchester and Cheshire Cancer Network
CHKS Ltd	Greater Midlands Cancer Network
Clarity Informatics Ltd	Grunenthal Ltd
Clatterbridge Centre for Oncology	Guerbet Laboratories Ltd
CLIC Sargent	Guildford & Waverley Primary Care Trust
Cochrane Bone, Joint and Muscle Trauma Group	Hammersmith and Fulham Primary Care Trust
College of Occupational Therapists	Hayward Medical Communications
Coloplast Limited	Health Quality Improvement Partnership
Commission for Social Care Inspection	Healthcare Improvement Scotland
Community District Nurses Association	Help the Hospices
Countess of Chester Hospital NHS Foundation Trust	Hindu Council UK
Covidien Ltd.	Hockley Medical Practice
Croydon Health Services NHS Trust	Hull and East Yorkshire Hospitals NHS Trust
Dako UK Ltd	Humber and Yorkshire Coast Cancer Network
David Lewis Centre, The	Humber NHS Foundation Trust
Deltex Medical	Imaging Equipment Ltd
Dendreon	Independent Healthcare Advisory Services
Department of Health	Institute of Biomedical Science
Department of Health, Social Services and Public Safety - Northern Ireland	Integrity Care Services Ltd.
Derby-Burton Cancer Network	Intra-Tech Healthcare Ltd
Dorset Primary Care Trust	Ipsen Ltd
Dudley Primary Care Trust	iQudos
Durham University	Isabel Hospice
East and North Hertfordshire NHS Trust	James Whale Fund for Kidney Cancer
East Midlands Cancer Network	Janssen
EDAP SA	JBOL Ltd
Endocare, Inc.	Johnson & Johnson

Equalities National Council	KCARE
Essex Cancer Network	KCI Medical Ltd
Kettering General Hospital	National Treatment Agency for Substance Misuse
Kidney Research UK	Newcastle upon Tyne Hospitals NHS Foundation Trust
King George Hospital	NHS Bath & North East Somerset
King's College Hospital NHS Foundation Trust	NHS Bournemouth and Poole
Lancashire Care NHS Foundation Trust	NHS Bromley
Latex Allergy Support Group	NHS Connecting for Health
Leeds Primary Care Trust (aka NHS Leeds)	NHS Cornwall and Isles Of Scilly
Leeds Teaching Hospitals NHS Trust	NHS County Durham and Darlington
Leicestershire County and Rutland Primary Care Trust	NHS Derbyshire county
Leicestershire, Northamptonshire and Rutland Cancer Network	NHS Direct
Lesbian & Gay Foundation	NHS England
Lesbian, gay, bisexual and trans domestic abuse forum	NHS Improvement
Link Pharmaceuticals	NHS Kirklees
Livability Icanho	NHS London
London Cancer	NHS Lothian
Luton and Dunstable Hospital NHS Trust	NHS National Cancer Screening Programmes
Macmillan Cancer Support	NHS Plus
Maidstone and Tunbridge Wells NHS Trust	NHS Warwickshire Primary Care Trust
Medicines and Healthcare products Regulatory Agency	NHS West Kent
Medway NHS Foundation Trust	NICE - Centre for Evidence based Purchasing
Men's Health Forum	NICE - CPHE
Merck Sharp & Dohme UK Ltd	NICE - Guidelines HE for info
Mid Cheshire Hospitals NHS Trust	NICE - IMPLEMENTATION CONSULTANT Region - East
Mid Yorkshire Hospitals NHS Trust	NICE - IMPLEMENTATION CO-ORDINATION for info
Milton Keynes NHS Foundation	NICE - Medicines and Prescribing Centre
Ministry of Defence	NICE - NHS Evidence
National Cancer Action Team	NICE - PPIP
National Cancer Intelligence Network	NICE - R&D for info
National Cancer Network Clinical Directors Group	NICE - Technical Appraisals
National Cancer Research Institute	NICE technical lead
National Clinical Guideline Centre	Norfolk & Waveney Prostate Cancer Support
National Collaborating Centre for Mental Health	North and East London Commissioning Support Unit
National Collaborating Centre for Women's and Children's Health	North East London Cancer Network
National Council for Palliative Care	North Trent Cancer Network
National Institute for Health Research Health Technology Assessment Programme	North Yorkshire & York Primary Care Trust

National Kidney Research Foundation	Northern Ireland Cancer Network
National Osteoporosis Society	Nottingham City Council
National Patient Safety Agency	Nottingham City Hospital
National Public Health Service for Wales	Nottinghamshire Healthcare NHS Trust
National Radiotherapy Implementation Group	Nova Healthcare
Novartis Pharmaceuticals	Royal College of Surgeons of England
NS Technomed	Royal Pharmaceutical Society
Nucletron	Royal Society of Medicine
Nutrition Society	Royal Surrey County Hospital NHS Trust
Oncura Ltd	Royal United Hospital Bath NHS Trust
Orion Pharma	Royal West Sussex NHS Trust
Ovarian Cancer Action	Sandoz Ltd
Oxford Health NHS Foundation Trust	Sandwell Primary Care Trust
Oxford Nutrition Ltd	Sanofi
Oxfordshire Primary Care Trust	Schering Health Care Ltd
Pan Birmingham Cancer Network	Scottish Intercollegiate Guidelines Network
Parenteral and Enteral Nutrition Group	Serono
Peninsula Cancer Network	Sexual Advice Association
PERIGON Healthcare Ltd	Sheffield Primary Care Trust
Pfizer	Sheffield Teaching Hospitals NHS Foundation Trust
pH Associates Ltd	Shropshire & Mid Wales Cancer Forum
Pharmametrics GmbH	Siemens Medical Solutions Diagnostics
Pharmion Limited	SNDRi
Pilgrims Hospices in East Kent	Social Care Institute for Excellence
Primary Care Pharmacists Association	Society and College of Radiographers
Prostate Brachytherapy Advisory Group	South London & Maudsley NHS Trust
Prostate Cancer Network	South Staffordshire Primary Care Trust
Prostate Cancer Support Federation	South Wales Cancer Network
Prostate Cancer UK	South West Yorkshire Partnership NHS Foundation Trust
Public Health Wales NHS Trust	Speciality European Pharma
Rarer Cancers Foundation	St Mary's Hospital
Roche Diagnostics	Step4Ward Adult Mental Health
Roche Products	Sue Ryder
Rotherham Primary Care Trust	Surrey, West Sussex and Hampshire Cancer Network
Royal Berkshire NHS Foundation Trust	Sussex Cancer Network
Royal College of General Practitioners	Sutton1in4 Network
Royal College of General Practitioners in Wales	Takeda UK Ltd
Royal College of Midwives	Tameside Hospital NHS Foundation Trust
Royal College of Nursing	Taunton Road Medical Centre
Royal College of Obstetricians and Gynaecologists	Teva UK
Royal College of Paediatrics and Child Health	Thames Valley Cancer Network
Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition	The Association for Cancer Surgery
Royal College of Pathologists	The Association for Clinical Biochemistry &

	Laboratory Medicine
Royal College of Physicians	The Association of the British Pharmaceutical Industry
Royal College of Physicians and Surgeons of Glasgow	The British In Vitro Diagnostics Association
Royal College of Psychiatrists	The National Association of Assistants in Surgical Practice
Royal College of Radiologists	The National LGB&T Partnership
Royal College of Surgeons of Edinburgh	The Princess Alexandra Hospital NHS Trust
The Rotherham NHS Foundation Trust	Velindre Hospital, Cardiff
Torbay and Southern Devon Health and Care NHS Trust	Velindre NHS Trust
Translucency Ltd.	Walsall Teaching Primary Care Trust
UCL Partners	Welsh Cancer Services Coordinating Group
UK Anaemia	Welsh Government
UK National Screening Committee	Wessex Cancer Trust
UK Specialised Services Public Health Network	West Midlands Ambulance Service NHS Trust
UKHIFU Limited	Western Cheshire Primary Care Trust
United Kingdom Council for Psychotherapy	Western Sussex Hospitals NHS Trust
United Kingdom National External Quality Assessment Service	Westminster Local Involvement Network
United Lincolnshire Hospitals NHS	Whipps Cross University Hospital NHS Trust
University College London Hospital NHS Foundation Trust	Wiltshire Primary Care Trust
University Hospital Aintree	World Cancer Research Fund
University Hospital Birmingham NHS Foundation Trust	York Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust	Yorkshire & The Humber Specialised Commissioning Group
University Hospitals Coventry and Warwickshire NHS Trust	Yorkshire Cancer Network
University of Nottingham	

1

2

I.3 Individuals carrying out 2014 literature reviews and complementary work

Update 2014

Overall Co-ordinators	
Dr John Graham	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Angela Bennett	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff
Project Managers	
Victoria Titshall[tt]	National Collaborating Centre for Cancer, Cardiff
Jenny Stock[uu]	National Collaborating Centre for Cancer, Cardiff
Senior Researcher	
Dr Nathan Bromham	National Collaborating Centre for Cancer, Cardiff
Researchers	
Kimberley Cann	National Collaborating Centre for Cancer, Cardiff
Mia Schmidt-Hansen	National Collaborating Centre for Cancer, Cardiff
Jennifer Hilgart	National Collaborating Centre for Cancer, Cardiff
Information Specialists	
Elise Hasler	National Collaborating Centre for Cancer, Cardiff
Stephanie Arnold	National Collaborating Centre for Cancer, Cardiff
Sabine Berendse	National Collaborating Centre for Cancer, Cardiff
Bernadette Coles	Site Librarian, Cancer Research Wales Library
Health Economist	
Matthew Prettyjohns	National Collaborating Centre for Cancer, Cardiff
Needs Assessment	
Kimberley Cann	National Collaborating Centre for Cancer, Cardiff
Matthew Jefferies	Cardiff School of Medicine

tt From February 2012 to December 2012
uu From December 2012 to January 2014

I.4 Members of the 2008 Guideline Development Group

GDG Chair	
Professor Mark Baker	The Lead Cancer Clinician, The Leeds Teaching Hospitals
GDG Lead Clinician	
Dr John Graham	Consultant Lead Clinical Oncologist, Taunton and Somerset NHS Trust
Group Members	
Philip Barnard	Patient/Carer Representative, Honorary Secretary, PSA Prostate Cancer Support Association
Angela Billington	Specialist Nurse, Director of Continence Services, Bournemouth and Poole PCT
Dr Brendan Carey	Consultant Radiologist, Cookridge Hospital, Leeds
Mr David Gillatt	Consultant Urologist, Southmead Hospital, Bristol
Jane Gosling	Consultant Nurse – Urology, Derriford Hospital, Plymouth
Dr Chris Hiley	Patient/Carer Representative, Head of Policy and Research Management, The Prostate Cancer Charity
Margaret Jewitt	Superintendent Radiographer, Western Park Hospital, Sheffield
Mr John McLoughlin	Consultant Urologist, West Suffolk Hospital Bury Edmunds and Honorary Consultant Urologist, Addenbrooke's Hospital Cambridge
Dr Chris Parker	Consultant in Clinical Oncology, Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton
John Rawlinson	Patient/Carer Representative, Senior Lecturer/Academic Lead in Mental Health, University of Plymouth
Professor David Weller	Head, General Practice, University of Edinburgh Primary Care
Dr John Wiles	Consultant in Palliative Medicine, Bromley Hospitals NHS Trust

1 **Declarations of Interest**

2 The Guideline Development Group were asked to declare any possible conflicts of interest
3 which could interfere with their work on the guideline.

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Mark Baker (Chair)	Consultancy work for Roche on high-level Dept of Health policy on cancer about unrestricted grants	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the work was not specific to prostate cancer or any of the drugs used in prostate cancer.
	Attended several advisory boards for Pharmion on thalidomide	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the advisory board was on an intervention that is not used in prostate cancer.
	Consultancy work for Pfizer on high-level Dept of Health policy on cancer about unrestricted grants	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the work was not specific to prostate cancer or any of the drugs used in prostate cancer.
John Graham (Lead Clinician)	Received fee from Speciality European Pharma for advisory work on aberalix in prostate cancer	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as this interventions is not being investigated by the guideline.
	Received travel, accommodation and expenses from Bayer Pharmaceuticals for attending an ECCO meeting in Paris	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.
	Received £500 honorarium + travel expenses from Sanofi- Aventis for giving an invited lecture to the NW Uro-Oncology Group	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the lecture was not specific to prostate cancer.
	Received travel and meeting expenses from Astra Zeneca for attending the ASCO Prostate Cancer Symposium in Feb 2006	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.
	Principal Investigator for multi- centre 3-arm randomised phase II trial of BIBF 1120 versus BIBW 2992 versus sequential administration of BIBF 1120 and BIBW 2992 in patients with hormone-resistant prostate cancer (Boehringer Ingelheim)	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the interventions included in the trial are not being investigated by the guideline.
	Principal Investigator for a trial on circulating tumour cell assay in men with	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the interventions included

GDG Member	Interest Declared	Type of Interest	Decisions Taken
	HRPC receiving chemotherapy (Immunicon)		in the trial are not being investigated by the guideline.
	Chief Investigator for UK in trial of GVAX (immunotherapy) vs docetaxel in HRPC (Cell Genesys)	Non-personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include docetaxel[vv] or GVAX[ww] as interventions.
	Chief Investigator for UK in trial of docetaxel vs LHRHa vs combination following radical prostatectomy (Sanofi Aventis)	Non-personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include docetaxel[xx]. Chairperson's action to be involved in discussions on LHRHa.
	Principal Investigator for a trial on satraplatin + prednisolone vs prednisolone alone in patients with HRPC (GPC Biotech)	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics as the Principal Investigator does not have supervisory responsibility for the work being undertaken.
	Trial set up meeting for alpha- radin in metastatic prostate cancer (Fulcrum Pharma)	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics as the interventions included in the trial are not being investigated by the guideline.
	Principal Investigator for trial of S-8184 in transitional cell carcinoma of urothelium (Sonus Pharmaceuticals)	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics as the trials are not specific to prostate cancer.
	Principal Investigator for a trial of VEG 102616 in metastatic renal cancer (GlaxoSmithKline)	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the trials are not specific to prostate cancer.
	Chief Investigator for UK for a trial of Sorafenib in metastatic renal cancer (Bayer Pharmaceuticals)	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the trials are not specific to prostate cancer.
	Received honorarium from Roche for attending an advisory board on bevacizumab in renal cancer	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the advisory board was not specific to prostate cancer.
Philip Barnard	Trustee of the Prostate Cancer Support Association	Personal non-pecuniary	Declare and can participate in discussions on all topics.
Angela Billington	Received honorarium from	Personal	Declare and can participate

vv Docetaxel was not included as an intervention in any of the topics discussed by the GDG. The recommendations on docetaxel were incorporated directly from NICE Technology Appraisal 101 in accordance with NICE procedures.

ww GVAX was not included as an intervention in any of the topics investigated by the guideline and was therefore not discussed by the GDG

GDG Member	Interest Declared	Type of Interest	Decisions Taken
	Pfizer for giving presentation on overactive bladder syndrome at the Sense of Leadership meeting in June 2007	pecuniary, non-specific	in discussions on all topics as the presentation given was not specific to prostate cancer.
	Received honorarium from Coloplast for giving presenta- tions on over-active bladder symptoms and catheterisation at nurse training days	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the presentation given was not specific to prostate cancer.
	Received honorarium from Rochester Medical Ltd for giving presentation on intermittent self catheterisation at Continence UK conference 2007. Also wrote an article on the same subject for Continence UK.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the presentation given was not specific to prostate cancer.
	Received honorarium from UCB Pharma for article on the transdermal patch for overactive bladder syndrome	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the presentation given was not specific to prostate cancer.
	Received a training pack for nurses (accredited by the RCN and sponsored by Pfizer)	Personal non-pecuniary	Declare and can participate in discussions on all topics.
Brendan Carey	Part of a team that received sponsorship from Oncura and IBT for mentoring new NHS sites set up to give brachytherapy. Money used for more brachytherapy research	Non-personal pecuniary, specific	Declare and can participate in discussion on all topics as the sponsorship went to the department to run research. Also brachytherapy is an intervention that is not specific to prostate cancer.
David Gillatt	Received educational and research grants from Astra Zeneca	Non-personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include interventions made by Astra Zeneca and used in prostate cancer (i.e. bicalutamide & goserelin acetate).
	Received sponsorship from Sanofi Aventis for travel, attendance and expenses to the European Society of Urological Oncology meeting	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.
	Observed and had training on the Ablatherm HIFU	Personal pecuniary,	Declare and must withdraw from discussions of any

GDG Member	Interest Declared	Type of Interest	Decisions Taken
	machine. Expenses reimbursed by EDAP	specific	topics that include HIFU as an intervention[xx].
	Received honorarium from Succinct Comms for attending an advisory board on docetaxel	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include docetaxel[xx] as an intervention.
Chris Parker	Received a fee from Algeta for speaking at a meeting	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as there are no interventions made by Algeta being investigated by the guideline.
	Received honorarium from Sanofi Aventis for giving educational talks on the role of docetaxel in HRPC	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include docetaxel1 as an intervention.
	Received honorarium from Cell Genesys for attending an advisory board on the G0034 trial (docetaxel +/- GVAX)	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include docetaxel[xx] or GVAX[yy] as interventions.
	Consultancy work for Algeta	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as there are no interventions made by Algeta being investigated by the guideline.
	Principal investigator for a cohort study on active surveillance	Personal non-pecuniary	Declare and can participate in all discussions as neither he nor his department receive any money for this.
	Chief investigator for MRC RADICALS trial which is studying the role of radiotherapy after surgery in prostate cancer	Personal non-pecuniary	Declare and can participate in all discussions as neither he nor his department receive any money for this.
John Wiles	Chairman and Executive Committee member of the Association for Palliative Medicine of GB & Ireland	Personal non-pecuniary	Declare and can participate in discussions on all topics.
	Medical Director Harris HospisCare	Personal non-pecuniary	Declare and can participate in discussions on all topics.
	Trustee of the National Council for Palliative Care	Personal non-pecuniary	Declare and can participate in discussions on all topics.
	Trustee and Company Director of the Care Not Killing Alliance	Personal non-pecuniary	Declare and can participate in discussions on all topics.
Jerviose Andreyev (Expert Advisor on	Educational grant from Norgine to run an ongoing study into the optimal	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the trials are not specific

xx The recommendations on HIFU had already been drafted by the time this interest occurred so a conflict does not exist

GDG Member	Interest Declared	Type of Interest	Decisions Taken
radiation toxicity)	treatment of radiotherapy-induced faecal incontinence		to prostate cancer.
	Educational grant from SHS International to run a study on the use of elemental diet in preventing acute and long term toxicity	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the trials are not specific to prostate cancer.

1
2

I.5 Organisations invited to comment on the 2008 guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

Abbott Laboratories Ltd (BASF/Knoll)	British Oncology Pharmacy Association
Addenbrooke's NHS Trust	British Prostate Group
Afiya Trust, The	British Psychological Society
Age Concern England	British Uro-oncology Group
Aintree Hospitals NHS Trust	Bromley PCT
Airedale General Hospital	BUPA
Albyn Medical Ltd	Cancer Black Care
American Medical Systems UK	Cancer Network Pharmacists Forum
Amgen UK Ltd	Cancer Research UK
Anglesey Local Health Board	Cancer Services Collaborative Improvement Partnership
Ashfield and Mansfield District PCT	CancerBACUP
Association for Continence Advice (ACA)	Cariad Technologies Ltd. CASPE
Association of Chartered Physiotherapists in Women's Health	Cephalon UK Ltd
Association of Clinical Biochemistry	Chartered Society of Physiotherapy
Association of the British Pharmaceuticals Industry (ABPI)	Clatterbridge Centre for Oncology NHS Trust
Astellas Pharma Ltd	College of Occupational Therapists
AstraZeneca UK Ltd	Coloplast Ltd
Aventis Pharma	Commission for Social Care Inspection
Bard Ltd	Connecting for Health Continence Foundation
Barnsley Acute Trust	Cornwall & Isles of Scilly PCT
Barnsley PCT	Countess of Chester Hospitals NHS Trust
Bath and North East Somerset PCT	Craven, Harrogate & Rural District PCT
Bedfordshire & Hertfordshire NHS Strategic Health Authority	DakoCytomation Ltd
Birmingham Heartlands & Solihull NHS Trust	David Lewis Centre, The
Blaenau Gwent Local Health Board	Denbighshire Local Health Board
Boehringer Ingelheim Ltd	Department of Health
Bostwick Laboratories	Dudley PCT
Bradford & Airedale PCT	EDAP-TMS
Bradford South & West PCT	Endocare Inc.
British Association for Counselling and Psychotherapy	Eisai Ltd
British Association of Art Therapists	Faculty of Public Health
British Association of Urological Nurses	Ferring Pharmaceuticals Ltd
British Association of Urological Surgeons	General Practice and Primary Care
British Dietetic Association	Gloucestershire Hospitals NHS Trust
British Geriatrics Society	Guerbet Laboratories Ltd
British Lymphology Society	Guildford & Waverley PCT Healthcare Commission

British National Formulary (BNF)	Help the Hospices
British Nuclear Medicine Society	
Independent Healthcare Advisory Service	Northwest London Hospitals NHS Trust
Intra-Tech Healthcare Ltd	Novartis Pharmaceuticals UK Ltd
Ipsen Ltd	Nucletron B.V.
James Whale Fund for Kidney Cancer	Nutrition Society
JBOL Ltd	Oncura International
Johnson & Johnson Medical	Ortho Biotech
King's College Hospital NHS Trust	Oxford Nutrition Ltd
King George's Hospital NHS Trust	Ovarian Cancer Action
Leeds North East PCT	PCaSO
Leeds PCT	Prostate Cancer Network
Leeds Teaching Hospitals NHS Trust	PERIGON (formerly the NHS Modernisation Agency)
Link Pharmaceuticals	Pharmion Ltd
Liverpool PCT	Pierre Fabre Ltd
Long Term Medical Conditions Alliance	Primary Care Pharmacists' Association
Luton and Dunstable Hospital NHS Trust	Princess Alexandra Hospital NHS Trust
Macmillan Cancer Relief	Prostate Brachytherapy Advisory Group
Maidstone and Tunbridge Wells NHS Trust	Prostate Cancer Charity, The
Medical Research Council Clinical Trials Unit	Prostate Cancer Research Foundation, The
Medicines and Healthcare Products Regulatory Agency	PSA Prostate Cancer Support Association
Medway NHS Trust, The	Prostate Cancer Support Federation
Men's Health Forum	Pfeizer Ltd
MERCK SHARP & DOHME	Queen Victoria Hospital NHS Foundation Trust
National Audit Office	Regional Public Health Group - London
National Association of Assistants in Surgical Practice	Roche Diagnostics Ltd
National Cancer Network Clinical Directors Group	Roche Products Ltd
National Cancer Research Institute (NCRI) Clinical Studies Group	Rotherham PCT
National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)	Royal College of Anaesthetists
National Council for Palliative Care	Royal College of General Practitioners
National Kidney Research Fund	Royal College of General Practitioners Wales
National Osteoporosis Society	Royal College of Nursing (RCN) Royal College of Pathologists
National Patient Safety Agency	Royal College of Physicians of London
National Public Health Service – Wales	Royal College of Psychiatrists
NCCHTA	Royal College of Radiologists
NHS Cancer Screening Programme	Royal College of Surgeons of England
NHS Direct	Royal Society of Medicine
NHS Health and Social Care Information Centre	Royal West Sussex Trust, The
NHS Quality Improvement Scotland	Royal United Hospital Bath NHS Trust
North East London Strategic Health Authority	Salford PCT
North Eastern Derbyshire PCT	Sandwell PCT

North Sheffield PCT	Sanofi-Synthelabo
North Trent Cancer network	
Schering Health Care Ltd	West Cornwall PCT
Scottish Intercollegiate Guidelines Network (SIGN)	West Lincolnshire PCT
Serono Ltd	Western Cheshire PCT
Sheffield South West PCT	Whipps Cross University Hospital NHS Trust
Sheffield Teaching Hospitals NHS Trust	Wiltshire PCT
Shropshire County and Telford & Welkin PCT	Wirral Hospital NHS Trust
Siemens Medical Solutions Diagnostics	World Cancer Research Fund International
Society and College of Radiographers	Wyeth Pharmaceuticals
South Asian Health Foundation	Yamanouchi Pharma Ltd
South East Sheffield PCT	Yorkshire and the Humber Commissioning Group
South West Kent PCT	University Hospital Aintree
Staffordshire Moorlands PCT	University Hospital Birmingham NHSFT
Stockport PCT	University Hospitals Coventry & Warwickshire NHS Trust
Sussex Cancer Network	University of Birmingham, Department of Primary Care & General Practice
Tameside and Glossop PCT	University of North Durham
Taunton Road Medical Centre	Velindre NHS Trust
Thames Valley Strategic Health Authority	Walsall PCT
Thames Valley Cancer Network	Walsall Teaching PCT
UK Anaemia	Wareney PCT
UK National Screening Committee	Welsh Assembly Government
UKHIFU	Wessex Cancer Trust
University College London Hospitals NHS Trust (UCLH)	

1
2

I.6 Individuals carrying out 2008 literature reviews and complementary work

Overall Co-ordinators	
Dr Fergus Macbeth	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Project Managers	
Angela Bennett[yy]	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff
Victoria Titshall[zz]	National Collaborating Centre for Cancer, Cardiff
Senior Researcher	
Angela Melder	National Collaborating Centre for Cancer, Cardiff
Researchers	
Dr Nathan Bromham	National Collaborating Centre for Cancer, Cardiff
Dr Rossela Stoicescu	External Reviewer
Dr Susanne Hempel	External Reviewer
Dr Ailsa Snaith	External Reviewer
Information Specialists	
Stephanie Arnold	National Collaborating Centre for Cancer, Cardiff
Sabine Berendse	National Collaborating Centre for Cancer, Cardiff
Elise Collins	National Collaborating Centre for Cancer, Cardiff
Health Economists	
Dr Alec Miners[aaa]	Lecturer in Health Economics, London School of Health and Tropical Medicine
Dr Dyfrig Hughes[bbb]	Director, Centre for the Economics and Policy in Health, University of Wales, Bangor
Dr Rhiannon Tudor Edwards[ddd]	Director, Centre for the Economics and Policy in Health, University of Wales, Bangor
Pat Linck[ddd]	Research Officer, Centre for the Economics and Policy in Health, University of Wales, Bangor
Eugenia Priedane[ddd]	Research Fellow, Centre for the Economics and Policy in Health, University of Wales, Bangor
Needs Assessment	
Dr Sean McPhail[ccc]	Head of Cancer Analysis, Cancer Intelligence Service South West Public Health Observatory
Dr Tanya Cross[ddd]	South West Public Health Observatory

yy From Nov 2005 to December 2006
zz From January 2007
aaa From Aug 2006
bbb From Nov 2005 to July 2006

I.7 Expert advisers to the 2008 Guideline Development Group

Dr Jervoise Andreyev	Consultant Gastroenterologist in Pelvic Radiation Disease, Department of Medicine, The Royal Marsden NHS Foundation Trust
Dr Clare Moynihan	The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust

I.8 Members of the2008 Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The members of the Guideline review Panel were as follows.

John Hyslop (Chair)	Consultant Radiologist, Royal Cornwall Hospital NHS Trust
Ash Paul	Deputy Medical Director, Health Commission Wales (Specialist Services)
Jon Seddon	Lay representative
Jonathan Hopper	Medical Director (UK and Ireland), ConvaTec