Prostate cancer:
diagnosis and treatment

Full Guideline
February 2008
Developed for NICE by the National Collaborating Centre for Cancer
Prostate cancer:
diagnosis and treatment

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Foreword

This is the first clinical guideline, rather than cancer service guidance, produced by the National Collaborating Centre for Cancer (NCC-C) and deals with a very common cancer. Its management often presents men and their health professionals with difficult decisions about the most appropriate treatment and we hope that this document will provide helpful and appropriate guidance. There are many areas where the research evidence is inadequate or incomplete and so some recommendations are based on the judgements and consensus of the guideline development group (GDG) using the best available evidence. We hope that the recommendations for further research will be taken up urgently by national research bodies and provide more robust evidence for the future.

I am very grateful for all the hard work and common sense of the members of the GDG, especially the patient and carer representatives, whose views helped significantly in shaping the document. I would also like to thank Professor Mark Baker, Chair, and Dr John Graham, Lead Clinician, whose skill, knowledge and commitment steered the project to a successful completion and all NCC-C staff for their hard work and support.

Dr Fergus Macbeth
NCC-C Director
Key priorities

1. Healthcare professionals should 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. Healthcare professionals should support men and their partners or carers in making treatment decisions, taking into account the effects on quality of life as well as survival.

2. To help men decide whether to have a prostate biopsy, healthcare professionals should 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 and Caribbean ethnicity) and any history of a previous negative prostate biopsy. The serum PSA level alone should not automatically lead to a prostate biopsy.

3. Men with low-risk localised prostate cancer who are considered suitable for radical treatment should first be offered active surveillance.

4. Men undergoing radical external beam radiotherapy for localised prostate cancer should receive a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction.

5. Healthcare professionals should ensure that men and their partners should have early and ongoing access to specialist erectile function services.

6. Healthcare professionals should 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.

7. Healthcare professionals should refer men with intractable stress incontinence to a specialist surgeon for consideration of an artificial urinary sphincter.

8. Biochemical relapse (a rising PSA) alone should not necessarily prompt an immediate change in treatment.

9. Hormonal therapy is not routinely recommended for 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.

10. When men with prostate cancer develop biochemical evidence of hormone-refractory disease, their management options should be discussed by the urological multidisciplinary team with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate.

11. Healthcare professionals should 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.

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1 This may also apply to some men with locally advanced prostate cancer.
Key research recommendations

1. 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.

The greatest uncertainties in managing prostate cancer are around 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.

2. Research is required into the clinical 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), cryotherapy and high intensity focused ultrasound, as well as combinations of surgery and radiotherapy with hormonal therapy and chemotherapy. The endpoints should include survival, local recurrence, toxicity and quality of life outcomes.

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 disease or localised recurrent disease.
Chapter 2: Communication and Support

The recommendations on communication and patient-centred care made in the two NICE cancer service guidance documents ‘Improving outcomes in urological cancers’ (2002) and ‘Improving supportive and palliative care for adults with cancer’ (2004) should be followed throughout the patient journey.

Men with prostate cancer should be offered 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).

Men with prostate cancer should be offered advice on how to access information and support from websites (for example, UK Prostate Link - www.prostate-link.org.uk), local and national cancer information services, and from cancer support groups.

Before choosing or recommending information resources for men with prostate cancer, healthcare professionals should check that their content is clear, reliable and up to date.

Healthcare professionals should seek feedback from men with prostate cancer and their carers to identify the highest quality information resources.

Healthcare professionals caring for men with prostate cancer should ascertain the extent to which the man wishes to be involved in decision making and ensure that he has sufficient information to do so.

A validated, up-to-date decision aid is recommended for use in all urological cancer multidisciplinary teams (MDTs). It should be offered to men with localised prostate cancer when making treatment decisions, by healthcare professionals trained in its use1.

Healthcare professionals should 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.

Healthcare professionals should 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.

Healthcare professionals should 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. Healthcare professionals should support men and their partners or carers in making treatment decisions, taking into account the effects on quality of life as well as survival.

Healthcare professionals should 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.

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1 A decision aid for men with localised prostate cancer is in development in the UK by the Urology Informed Decision Making Steering Group (publication expected 2008).
Chapter 3: Diagnosis and Staging of Prostate Cancer

Biopsy

To help men decide whether to have a prostate biopsy, healthcare professionals should 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 and black Caribbean ethnicity) and any history of a previous negative prostate biopsy. The serum PSA level alone should not automatically lead to a prostate biopsy.

Men and their partners or carers should be given information, support and adequate time to decide whether or not they wish to undergo prostate biopsy. The information should 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.

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), prostate biopsy for histological confirmation should not be performed, unless this is required as part of a clinical trial.

Healthcare professionals should carry out prostate biopsy following the procedure recommended in ‘Undertaking a transrectal ultrasound guided biopsy of the prostate’ (PCRMP 2006). The results of all prostate biopsies should be reviewed by a urological cancer MDT. Men should only be re-biopsied following a negative biopsy after an MDT review of the risk characteristics including life expectancy, PSA, DRE and prostate volume.

Men should decide whether or not to have a re-biopsy following a negative biopsy, having had the risks and benefits explained to them.

Imaging

<table>
<thead>
<tr>
<th>Table A Risk stratification for men with localised prostate cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
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<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Low risk</td>
</tr>
<tr>
<td>Intermediate risk</td>
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<tr>
<td>High risk</td>
</tr>
</tbody>
</table>

Healthcare professionals should determine the provisional treatment intent (radical or non-radical) before decisions on imaging are made.

Imaging is not routinely recommended for men in whom no radical treatment is intended.

Computerised tomography (CT) of the pelvis is not recommended for men with low- or intermediate-risk localised prostate cancer (see table A).

Men with high-risk localised (see table A) and locally advanced prostate cancer who are being considered for radical treatment should have pelvic imaging with either magnetic resonance imaging (MRI), or CT if MRI is contraindicated.

Magnetic resonance spectroscopy is not recommended for men with prostate cancer except in the context of a clinical trial.

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3 Clinical stage T3-T4 represents locally advanced disease.
Isotope bone scans are not routinely recommended for men with low-risk localised prostate cancer.

Isotope bone scans should be performed when hormonal therapy is being deferred through watchful waiting in asymptomatic men who are at high risk of developing bone complications.

Positron emission tomography imaging for prostate cancer is not recommended in routine clinical practice.

**Nomograms**

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.

When nomograms are used, healthcare professionals should clearly explain the reliability, validity and limitations of the prediction.

**Chapter 4: Localised Prostate Cancer**

**Watchful waiting and active surveillance**

Urological cancer MDTs should assign a risk category (see table A) to all newly diagnosed men with localised prostate cancer.

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) should be reviewed by a member of the urological cancer MDT.

Men with low-risk localised prostate cancer (see table A) who are considered suitable for radical treatment should first be offered active surveillance.

Active surveillance is particularly suitable for a subgroup of men with low-risk localised prostate cancer who have clinical stage T1c, a Gleason score 3+3, a PSA density < 0.15 ng/ml/ml and who have cancer in less than 50% of their total number of biopsy cores with < 10mm of any core involved.

Active surveillance should be discussed as an option with men who have intermediate-risk localised prostate cancer (see table A).

Active surveillance is not recommended for men with high-risk localised prostate cancer.

To reduce the sampling error associated with prostate biopsy, men who are candidates for active surveillance should have at least 10 biopsy cores taken.

Active surveillance should include at least one re-biopsy and may be performed in accordance with the ProSTART protocol.

Men with localised prostate cancer who have chosen an active surveillance regimen and who have evidence of disease progression (that is, a rise in PSA or adverse findings on biopsy) should be offered radical treatment.

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.

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Radical treatment

Healthcare professionals should offer radical prostatectomy or radical radiotherapy (conformal) to men with intermediate-risk localised prostate cancer.

Healthcare professionals should offer radical prostatectomy or radical radiotherapy (conformal) to men with high-risk localised prostate cancer where there is a realistic prospect of long-term disease control (see recommendations in Chapter 6).

Brachytherapy is not recommended for men with high-risk localised prostate cancer.

Clinical oncologists should use conformal radiotherapy for men with localised prostate cancer, receiving radical external beam radiotherapy.

Men undergoing radical external beam radiotherapy for localised prostate cancer should receive a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction.

Adjuvant hormonal therapy is recommended for a minimum of 2 years in men receiving radical radiotherapy for localised prostate cancer who have a Gleason score of ≥ 8.

High intensity focused ultrasound (HIFU) and cryotherapy are not recommended for men with localised prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions.

Managing adverse effects of treatment

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.

Men presenting with symptoms consistent with radiation-induced enteropathy should be fully investigated (including using flexible sigmoidoscopy) to exclude inflammatory bowel disease or malignancy of the large bowel and to ascertain the nature of the radiation injury. Particular caution should be taken with anterior wall rectal biopsy following brachytherapy because of the risk of fistulation.

Men treated with radical radiotherapy for prostate cancer should be offered flexible sigmoidoscopy every 5 years.

Steroid enemas should not be used for treating men with radiation proctopathy.

The nature and treatment of radiation-induced injury to the gastrointestinal tract should be included in the training programmes for oncologists and gastroenterologists.

Prior to treatment, men and their partners should be warned that treatment for prostate cancer will result in an alteration of sexual experience, and may result in loss of sexual function.

Men and their partners should be warned about the potential loss of ejaculation and fertility associated with treatment for prostate cancer. Sperm storage should be offered.

Healthcare professionals should ensure that men and their partners have early and ongoing access to specialist erectile dysfunction services.

Men with prostate cancer who experience loss of erectile function should be offered phosphodiesterase type 5 (PDE5) inhibitors to improve their chance of spontaneous erections.

If PDE5 inhibitors fail to restore erectile function or are contraindicated, men should be offered vacuum devices, intraurethral inserts or penile injections, or penile prostheses as an alternative.

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5 This may also apply to some men with locally advanced prostate cancer.

6 This may also apply to some men with locally advanced prostate cancer.

7 NICE interventional procedures guidance 130, 230 and 259 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.
Men experiencing troublesome urinary symptoms before treatment should be offered a urological assessment.

Men undergoing treatment for prostate cancer should be warned of the likely effects of the treatment on their urinary function.

Healthcare professionals should ensure that men with troublesome urinary symptoms after treatment should 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.

Healthcare professionals should refer men with intractable stress incontinence to a specialist surgeon for consideration of an artificial urinary sphincter.

The injection of bulking agents into the distal urinary sphincter is not recommended to treat stress incontinence.

**Follow-up**

Healthcare professionals should discuss the purpose, duration, frequency and location of follow-up with each man with localised prostate cancer, and if he wishes, his partner or carers.

Men with prostate cancer should be clearly advised about potential longer term adverse effects and when and how to report them.

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.

PSA levels for all men with prostate cancer who are having radical treatment should be checked 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.

Routine DRE is not recommended in men with prostate cancer while the PSA remains at baseline levels.

After at least 2 years, men with a stable PSA and who have had no significant treatment complications, should be offered follow-up outside hospital (for example, in primary care) by telephone or secure electronic communications, unless they are taking part in a clinical trial that requires more formal clinic-based follow-up. Direct access to the urological cancer MDT should be offered and explained.

**Chapter 5: Managing Relapse After Radical Treatment**

Analyse serial PSA levels after radical treatment using the same assay technique.

Biopsy of the prostatic bed should not be performed in men with prostate cancer who have had a radical prostatectomy.

Biopsy of the prostate after radiotherapy should only be performed in men with prostate cancer who are being considered for local salvage therapy in the context of a clinical trial.

For men with evidence of biochemical relapse following radical treatment and who are considering radical salvage therapy:

- Routine MRI scanning should not be performed prior to salvage radiotherapy in men with prostate cancer
- Perform an isotope bone scan if symptoms or PSA trends are suggestive of metastases.

Biochemical relapse (a rising PSA) alone should not necessarily prompt an immediate change in treatment.

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*This may also apply to some men with locally advanced prostate cancer.*
Biochemical relapse should trigger an estimate of PSA doubling time, based on a minimum of 3 measurements over at least a 6 month period.

Men with biochemical relapse after radical prostatectomy, with no known metastases, should be offered early radical radiotherapy to the prostatic bed.

Men with biochemical relapse should be considered for entry to appropriate clinical trials.

Hormonal therapy is not routinely recommended for 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.

**Chapter 6: Locally Advanced Prostate Cancer**

**Systemic treatment**

Neoadjuvant and concurrent luteinising hormone-releasing hormone agonist (LHRHa) therapy is recommended for 3 to 6 months in men receiving radical radiotherapy for locally advanced prostate cancer.

Adjuvant hormonal therapy in addition to radical prostatectomy is not recommended, even in men with margin-positive disease, other than in the context of a clinical trial.

Adjuvant hormonal therapy is recommended for a minimum of 2 years in men receiving radical radiotherapy for locally advanced prostate cancer who have a Gleason score of ≥ 8.

Bisphosphonates should not be used for the prevention of bone metastases in men with prostate cancer.

**Radiotherapy**

Clinical oncologists should consider pelvic radiotherapy in men with locally advanced prostate cancer who have a > 15% risk of pelvic lymph node involvement who are to receive neoadjuvant hormonal therapy and radical radiotherapy.

Immediate post-operative radiotherapy after radical prostatectomy is not routinely recommended, even in men with margin-positive disease, other than in the context of a clinical trial.

HIFU and cryotherapy are not recommended for men with locally advanced prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions.

**Chapter 7: Metastatic Prostate Cancer**

**Hormonal therapy**

Healthcare professionals should offer bilateral orchidectomy to all men with metastatic prostate cancer as an alternative to continuous LHRHa therapy.

Combined androgen blockade is not recommended as a first-line treatment for men with metastatic prostate cancer.

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9 For example RADICALS (www.ctu.mrc.ac.uk/studies/PR10.asp)
10 For example RADICALS (www.ctu.mrc.ac.uk/studies/PR10.asp)
11 Estimated using the Roach formula: %LN risk = 0.2/SPA + (10x(Gleason score - 6))
12 For example RADICALS (www.ctu.mrc.ac.uk/studies/PR10.asp)
13 NICE interventional procedures guidance 130, 230 and 259 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.
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, anti-androgen monotherapy with bicalutamide (150 mg)\textsuperscript{14} is appropriate.

Healthcare professionals should begin androgen withdrawal and stop bicalutamide treatment in men with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function.

Intermittent androgen withdrawal may be offered to men with metastatic prostate cancer providing they are informed that there is no long-term evidence of its effectiveness.

**Managing the complications of hormonal therapy**

Synthetic progestogens (administered orally or parenterally) are recommended as first-line therapy for the management of troublesome hot flushes. If oral therapy is used, it should be given for 2 weeks, and re-started, if effective, on recurrence of symptoms.

Men starting long-term bicalutamide monotherapy (> 6 months) should receive prophylactic radiotherapy to both breast buds within the first month of treatment. A single fraction of 8 Gy using orthovoltage or electron beam radiotherapy is recommended.

If radiotherapy is unsuccessful in preventing gynaecomastia, weekly tamoxifen should be considered.

Inform men starting androgen withdrawal therapy that regular resistance exercise reduces fatigue and improves quality of life.

**Hormone-refractory prostate cancer**

When men with prostate cancer develop biochemical evidence of hormone-refractory disease, their treatment options should be discussed by the urological cancer MDT with a view to seeking an oncological and/or specialist palliative care opinion as appropriate.

Docetaxel is recommended, within its licensed indications, as a treatment option for men with hormone-refractory metastatic prostate cancer only if their Karnofsky performance-status score is 60\% or more\textsuperscript{15}.

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\textsuperscript{15}.

Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy\textsuperscript{15}.

A corticosteroid such as dexamethasone (0.5 mg daily) daily is recommended as third-line hormonal therapy after androgen withdrawal and anti-androgen therapy for men with hormone-refractory prostate cancer.

Men with hormone-refractory prostate cancer shown to have extensive metastases in the spine (for example, on a bone scan) should have spinal MRI if they develop any spinal related symptoms.

The routine use of spinal MRI for all men with hormone-refractory prostate cancer and known bone metastases is not recommended.

The use of bisphosphonates to prevent or reduce the complications of bone metastases in men with hormone-refractory prostate cancer is not recommended.

\textsuperscript{14} At the time of publication (February 2008) bicalutamide did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

\textsuperscript{15} These recommendations are from ‘Docetaxel for the treatment of hormone-refractory metastatic prostate cancer’ (NICE technology appraisal guidance 101).
Bisphosphonates for pain relief may be considered for men with hormone-refractory prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed. The oral or intravenous route of administration should be chosen according to convenience, tolerability and cost.

Bisphosphonates should not be used routinely to prevent osteoporosis in men with prostate cancer receiving androgen withdrawal therapy.

Strontium-89 should be considered for men with hormone-refractory prostate cancer and painful bone metastases, especially those men who are unlikely to receive myelosuppressive chemotherapy.

Decompression of the upper urinary tract by percutaneous nephrostomy or by insertion of a double J stent should be offered to men with obstructive uropathy secondary to hormone-refractory prostate cancer.

The option of no intervention should also be discussed with men with obstructive uropathy secondary to hormone-refractory prostate cancer and remains a choice for some.

**Palliative care**

Men with metastatic prostate cancer should be offered tailored information and access to specialist urology and palliative care teams to address the specific needs of men with metastatic cancer. They should have the opportunity to discuss any significant changes in their disease status or symptoms as these occur.

The regular assessment of needs should be applied systematically to men with metastatic prostate cancer.

Palliative interventions at any stage should be integrated into coordinated care, and any transitions between care settings should be facilitated as smoothly as possible.

Healthcare professionals should discuss personal preferences for palliative care as early as possible with men with metastatic prostate cancer, their partners and carers. Treatment/care plans should be tailored accordingly and the preferred place of care should be identified.

Healthcare professionals should 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.

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Methodology

Introduction

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.

Clinical guidelines for the NHS in England, Wales and Northern Ireland are produced as a response to a request from the Department of Health (DH). They approve topics for guideline development and before deciding whether to refer a particular topic to the National Institute for Health and Clinical Excellence (NICE) they consult with the relevant patient bodies, professional organisations and companies. Once a topic is referred, NICE then commissions one of seven National Collaborating Centres (NCCs) to produce a guideline. The Collaborating Centres are independent of government and comprise partnerships between a variety of academic institutions, health profession bodies and patient groups. The National Collaborating Centre for Cancer (NCC-C) was referred the topic of prostate cancer in October 2003 as part of NICE’s ninth wave work programme. However the guideline development process began officially on 10th November 2005 when sufficient capacity became available at the NCC-C.

Who is the Guideline Intended For?

This guideline does not include recommendations covering every detail of the diagnosis and treatment of prostate cancer. Instead we have tried to focus on those areas of clinical practice that are (i) 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

Guideline topics selected by the DH identify the main areas to be covered by the guideline in a specific remit. The following remit for this guideline was received as part of NICE’s ninth wave programme of work:

‘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 diagnostic and staging procedures – excluding screening
• the main treatment modalities including hormonal therapy (covering surgical and chemical castration)
• the role of tumour specific bisphosphonates.’

1 Since this remit was received, clinical guidelines now apply to Northern Ireland.
What the Guideline Covers - The Scope

The remit was then translated into a scope document by the Guideline Development Group (GDG) Chair and Lead Clinician and staff at the NCC-C. The purpose of the scope was to:

• provide an overview of what the guideline would include and exclude
• identify the key aspects of care that must be included
• 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 and the remit
• inform the development of the clinical questions and search strategy
• inform professionals and the public about the expected content of the guideline.

Prior to the commencement of the guideline development process, the scope was subject to a four week stakeholder consultation in accordance with processes established by NICE in the ‘NICE guidelines manual’ (NICE, 2005, NICE 2006, NICE 2007). The full scope is shown in Appendix 6. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from registered stakeholder organisations and the NICE Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed by the GRP; signed off by NICE and posted on the NICE website.

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 2007). 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 8.

Needs Assessment

As part of the guideline development process the NCC-C invited the National South West Public Health Observatory to undertake a needs assessment. The needs assessment aims to describe the burden of disease and current service provision for men with prostate cancer in England and Wales, which informed the development of the guideline. This document forms a supplement to the full guideline and will also appear on the accompanying CD-ROM to this 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.

The Process of Guideline Development – Who Develops the Guideline?

Overview

The development of this guideline was based upon methods outlined by the ‘NICE guidelines manual’. A team of health professionals, lay representatives and technical experts known as the GDG (see Appendix 8), 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, defined the scope which sets the parameters of the guideline
• forming the guideline development group
• developing clinical questions
• 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
• updating the guideline.

The Guideline Development Group (GDG)
The prostate cancer GDG was recruited in line with the existing NICE protocol as set out in the ‘NICE guidelines manual’. The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were informally interviewed 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. Requests for nominations were sent to the main stakeholder organisations and patient organisations/charities (see Appendix 8). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms, following nomination from their respective stakeholder organisation. 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 8).

Guideline Development Group Meetings
Thirteen GDG meetings were held between 10 November 2005 and 28 June 2007. During each GDG meeting (either held over one or two 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 prior to presenting it to 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 sub-groups 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 integral user focus to the GDG and the guideline development process. The GDG included three patient/carer representatives. 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 phase of the guideline 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 the guideline can be found in Appendix 8. All relevant position papers are presented as part of the evidence review and will also appear on the accompanying CD-ROM to this guideline.

**Developing Clinical Evidence-Based Questions**

**Background**

The scope, as described in Appendix 6, needs to be very clear about which patient groups are included and which areas of clinical care should be considered. But within these boundaries it does not usually specify which topics are considered a priority.

It was recognised by the NCC-C at an early stage that in order to complete the guideline development work to an appropriate standard the GDG needed to restrict its work to approximately 30 clinical questions. Previously this prioritisation would have been carried out by the GDG at its first two meetings but it was clear from some guidelines already published that this approach had resulted in a much larger number of questions than 30 being addressed.

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. It was therefore felt important that the 30 clinical questions should be prioritised into 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**

An extensive list of potential topics for the guideline to investigate was compiled by the NCC-C Director and GDG Chair and Lead Clinician in consultation with a small number of prostate cancer multidisciplinary teams across England and Wales.

This list was incorporated into a questionnaire which asked respondents to rate each topic on a five point Likert scale ranging from 0 (not a priority) to 5 (very high priority). It was made clear that respondents would be rating the priority for each topic to be included in a clinical guideline to be published in two years’ time. The questionnaire also asked respondents to suggest any additional topics they would like to see included with an equivalent assessment of their priority.

Questionnaires were subsequently sent to the Prostate Cancer Advisory Groups of all 37 cancer networks in England and Wales with a request for a 4-week turnaround. (A list of all cancer networks can be found on the Cancer Action Team website at the DH). Questionnaires were also sent via the Patient and Public Involvement Programme (PPIP) at NICE to all relevant patient/carer stakeholder organisations.

The scores from each completed questionnaire were aggregated by NCC-C staff and ranked. These results together with information on identifiable practice variation (see needs assessment) were presented to the GDG at its first meeting. The list of prioritised topics produced via the questionnaire survey was in no way definitive and the GDG used these results to agree their final priorities for the clinical questions.

For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: the patients (the population under study - P), the interventions (what is being done - I), the comparisons (other main treatment options - C) and the outcomes (the measures of how effective the interventions have been - O). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated.

The final list of clinical questions can be found in Appendix 7.
Care Pathway

Early in the development process the GDG drafted an outline care pathway (or algorithm) in order to explore how patients with prostate cancer might access and be dealt with by the NHS.

Review of Clinical Literature

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. Additionally, stakeholder organisations were invited to submit evidence for consideration by the GDG, provided it was relevant to the agreed list of clinical questions.

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, for example modeling (see section on ‘Incorporating Health Economic Evidence’).

Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence. Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when necessary. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:
- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1994 onwards
- Psychinfo 1806 onwards
- Web of Science 1970 onwards. [specifically Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI)]
- System for Information on Grey Literature In Europe (SIGLE) 1980–2005
- Biomed Central 1997 onwards
- National Research Register (NRR)
- Current Controlled Trials.

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

Searches were updated and re-run 6–8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, 1 June 2007 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 (and will also appear on the accompanying CD-ROM to this guideline).

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. The researcher then individually applied the inclusion/exclusion criteria to determine which studies would be relevant for inclusion and subsequent appraisal. Lists of excluded papers were generated for each question and the rationale for the exclusion was presented to the GDG when required.
The researcher then critically appraised the full papers. Critical appraisal checklists were compiled for each paper and one researcher undertook the critical appraisal and data extraction. The reviewer assessed the quality of eligible studies by referring to the SIGN quality checklist for systematic reviews/meta-analyses and randomised control trials (Table B). Evidence relating to clinical effectiveness was classified using this established hierarchical system. However this checklist is less appropriate for studies reporting diagnostic tests of accuracy. In the absence of a validated hierarchy for this type of test, NICE suggests levels of evidence that take into account the factors likely to affect the validity of these studies.

Table B  Levels of evidence for intervention studies. Data source: ‘NICE guidelines manual’ (NICE 2007).

<table>
<thead>
<tr>
<th>Level</th>
<th>Source of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1−</td>
<td>Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2−</td>
<td>Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytical studies (for example case reports, case series)</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion, formal consensus</td>
</tr>
</tbody>
</table>

For all the relevant appraised studies for a particular question, data on the type of population, intervention, comparator and outcomes (PICO) was recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All the evidence was considered carefully by the GDG for accuracy and completeness.

All procedures were fully compliant with NICE methodology as detailed in the ‘NICE guidelines manual’.

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.

**Incorporating Health Economics Evidence**

The aim of the economic input into the guideline was to inform the GDG of potential economic issues relating to prostate cancer. It is important to investigate whether health services are both clinically effective and cost effective, i.e. are they ‘value for money’.

The health economist helped the GDG by identifying priority topics within the guideline that might benefit from economic analysis, reviewing the available economic evidence and, where necessary, conducting economic analysis. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible.

In order to assess the cost-effectiveness of each priority topic, a comprehensive systematic review of the economic literature was conducted. 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 and quality of life filter.
Each search strategy was designed to find any applied study estimating the cost or cost effectiveness of the topic under consideration. A health economist reviewed abstracts and relevant papers were ordered for appraisal.

Published economic evidence was obtained from a variety of sources:
- Medline 1966 onwards
- Embase 1980 onwards
- NHS Economic Evaluations Database (NHS EED)
- EconLit 1969 onwards.

**Economic Modelling**

In addition to the review of the relevant clinical evidence, the GDG were required to determine whether or not the cost-effectiveness of each of the individual clinical questions should be investigated. After the clinical questions were decided, the GDG agreed which topics were an ‘economic priority’ for modeling. These ‘economic priorities’ were chosen on the basis of the following criteria, in broad accordance with the ‘NICE guidelines manual’:

**Overall Relevance of the Topic**
- *The number of patients affected*: interventions affecting relatively large numbers of patients were given a higher economic priority than those affecting fewer patients
- *The health benefits to the patient*: interventions that were considered to have a potentially significant impact on both survival and quality of life were given a higher economic priority
- *The per patient cost*: interventions with potentially high financial (cost/savings) implications were given higher priority compared to interventions expected to have lower financial implications
- *Likelihood of changing clinical practice*: priority was given to topics that were considered likely to represent a significant change to existing clinical practice.

**Uncertainty**
- *High level of existing uncertainty*: higher economic priority was given to clinical questions in which further economic analysis was considered likely to reduce current uncertainty over cost-effectiveness. Low priority was given to clinical questions when the current literature implied a clearly ‘attractive’ or ‘unattractive’ incremental cost-effectiveness ratio, which was regarded as generalisable to a UK healthcare setting
- *Likelihood of reducing uncertainty with further analyses (feasibility issues)*: when there was poor evidence for the clinical effectiveness of an intervention, then there was considered to be less justification for an economic analysis to be undertaken.

Once the economic priority clinical questions had been chosen, the next task was to perform a systematic review of the cost-effectiveness literature. When relevant published evidence was identified and considered to be of sufficient quality, this information was used to inform the recommendation for that specific clinical question. When no relevant cost-effectiveness evidence was identified, or when it was not considered to be of reasonable quality, consideration was given to building a de novo economic model. This decision was made by the GDG based on an assessment of the available evidence required to populate a potential economic model.

For those clinical questions where an economic model was required, the information specialist performed supplemental literature searches to obtain additional data for modeling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

The clinical question in this guideline selected for modeling was chosen because at the time it was considered likely that the recommendations under consideration could substantially change clinical practice in the NHS and have important consequences for resource use. The
details of the model are presented in the evidence review and Appendix 3. During the modeling process the following general principles were adhered to:

- the GDG Chair and Clinical Lead were consulted during the construction and interpretation of the model
- the model was based on the best evidence from the systematic review
- model assumptions were reported fully and transparently
- the results were subject to thorough sensitivity analysis and limitations discussed
- costs were calculated from a health services perspective.

**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 explicit in the accompanying qualifying statement.

**Qualifying Statements**

As clinical guidelines are currently formatted, there is limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost-effectiveness. To make this process more transparent to the reader, the NCC-C felt the need for an explicit, easily understood and consistent way of expressing the reasons for making each recommendation.

The way we have chosen to do this is by writing a ‘qualifying statement’ to accompany every recommendation and will usually cover:

- the strength of evidence about benefits and harms for the intervention being considered
- the degree of consensus within the GDG
- the costs and cost-effectiveness (if formally assessed by the health economics team).

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, eleven key priorities and two key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed (see pages xxvii-xxxiv for algorithms). To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

**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 (see Appendix 8) had one opportunity to comment on the draft guideline and this was posted on the NICE website between 31st July and 23rd September 2007. The GRP also reviewed the guideline and checked that stakeholder comments had been addressed.

Following the consultation period the GDG finalised the recommendations and the NCC-C produced the final document. This was then submitted to NICE for approval and 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 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
• the Quick Reference Guide (QRG), which is a summary of the main recommendations in the NICE guideline. This is available in hard copy via the NHS telephone response line (0870 1555 455).

• Understanding NICE Guidance (UNG), which describes the guideline using non-technical language. It is written chiefly for men with prostate cancer but may also be useful for family members, advocates or those who care for men with prostate cancer. This is available in hard copy via the NHS telephone response line (0870 1555 455).

Updating the Guideline

Literature searches were repeated for all of the clinical questions at the end of the GDG development process, allowing any relevant papers published before 1st June 2007 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will commission a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be updated approximately 4 years after publication.

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

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

References

Algorithms

A pictorial guide to show how the guideline is structured.

Prostate Cancer Pathway

Men referred with suspected prostate cancer

Diagnosis and staging

Treatment for localised, locally advanced or metastatic disease

Relapse  Follow-up  Complications and side effects

1 Referral guidelines for suspected cancer. NICE clinical guideline (2005)
Diagnosis and Staging

Man referred with suspected prostate cancer 1

Decision made to proceed to biopsy 2
Information and support to be provided before biopsy

Yes

MDT
- Review biopsy result
- Assign initial risk group
  - nomograms can be used
- Organise staging
  - radiological staging only after treatment intent is decided

No

Monitor PSA

Outpatient Clinic
- Offer appointment with specialist surgeon and oncologist
- Offer decision aids
- Information and support
  - treatment decisions should take account of quality of life as well as survival

Go to Localised disease, Locally advanced disease or Metastatic disease algorithms

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1 Referral guidelines for suspected cancer. NICE guideline (2005)
2 PCRMP Guidance on prostate biopsy
Localised Disease

(For the management of complications and side effects of treatment see algorithm on page xxxiii)

<table>
<thead>
<tr>
<th>Treatment Option</th>
<th>Low-risk men (PSA ≤ 10 ng/ml and Gleason score ≤ 6 and T1-T2a)</th>
<th>Intermediate risk men (PSA 10-20 ng/ml or Gleason score 7 or T2b-c)</th>
<th>High-risk men (PSA ≥ 20 ng/ml or Gleason score ≥ 8 or T3-T4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful waiting</td>
<td>◊</td>
<td>◊</td>
<td>◊</td>
</tr>
<tr>
<td>Active surveillance</td>
<td>✓</td>
<td>◊</td>
<td>❌</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>◊</td>
<td>◊</td>
<td>❌</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>◊</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Radical radiotherapy</td>
<td>◊</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
</tr>
<tr>
<td>HIFU</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
</tr>
</tbody>
</table>

- **Preferred treatment**
- **Treatment option**
- **Not recommended**
- **Not recommended other than in the context of clinical trials**

- Should be treatment of choice in low-risk men who are suitable for radical treatment
- Include at least 1 re-biopsy
- If evidence of disease progression men should be offered radical treatment

- Use conformal radiotherapy
- Minimum dose 74Gy
Locally Advanced Disease

For the management of complications and side effects of treatment see algorithm on page xxxiii

- T3a – T4 prostate cancer
  - Men receiving radical radiotherapy
    - Neoadjuvant hormonal therapy
    - Adjuvant hormonal therapy for up to 3 years
  - Hormonal therapy alone
    - See Metastatic Disease algorithm
  - Bisphosphonates Not recommended for prevention of bone metastases
- Post-radical prostatectomy with extracapsular spread
  - Men receiving radical prostatectomy
    - Immediate post-op radiotherapy not recommended
    - Adjuvant hormonal therapy not recommended
Follow-up and Relapse after Radical Treatment

**Follow-up:**
- Men on watchful waiting should be followed-up in primary care in accordance with locally agreed protocols
  - PSA should be measured at least annually
- After 2 years follow-up should be offered outside hospital (e.g. telephone, e-mail, primary care) to men with stable PSA and no significant treatment complications

**Relapse after radical treatment:**
- Biochemical relapse alone should not prompt treatment
- An isotope bone scan should be performed if symptoms or PSA trends are suggestive of metastases or radical salvage therapy is being considered

After radical radiotherapy or brachytherapy
- Clinical trials into comparative clinical and cost effectiveness of local salvage treatments such as cryotherapy and HIFU

**Hormonal therapy for:**
- Symptomatic local disease progression
- Metastases
- PSA doubling time <3 months

After radical prostatectomy
- Clinical trials should examine the role of local salvage treatment and systemic therapy

**Local salvage therapy:**
- Radiotherapy is recommended
Metastatic Disease

(For the management of complications and side effects of treatment see algorithm on page xxxiii)

**Newly diagnosed or relapsing**
Biopsy not required if high PSA and positive bone scan

**First line hormonal therapy**
- LHRHa or bilateral orchidectomy should be offered
- Intermittent androgen withdrawal may be offered
- Combined androgen blockade is not recommended

**Hormone refractory disease**
- Men with hormone refractory disease should be discussed at MDT and referred to oncology or palliative care if needed
- Palliative care should be available when needed not only at end of life

**Chemotherapy**
- Docetaxel if Karnofsky ≥ 60%
- Up to 10 cycles
- Repeat cycles not recommended
(From NICE health technology appraisal guidance 101)

**Corticosteroids**
e.g. Dexamethasone 0.5 mg daily
Management of Complications and Side Effects of Treatment

Complications of treatment

Radical prostatectomy
Men with urinary dysfunction should have access to specialist continence services

Radical radiotherapy
Men should be offered flexible sigmoidoscopy every 5 years after radiotherapy

Hormonal therapy
- Hot flushes should be treated with synthetic progestogens
- Androgen withdrawal therapy is a risk factor for the development of osteoporosis
- Consider prophylactic radiotherapy to prevent gynaecomastia

Complications of disease

Pelvic disease
- Men with obstructive uropathy secondary to HRPC should be offered decompression
- The option of no intervention should be discussed openly

Bone metastases
- Bisphosphonates are not recommended for the complications of bone metastases except uncontrolled pain
- Sr-89 should be considered
- Spinal MRI should be considered in men with hormone refractory disease and extensive bone metastases if they develop spinal related symptoms

Sexual dysfunction
Men and their partners should have early access to specialist erectile dysfunction services
1 Epidemiology

1.1 Introduction

Prostate cancer is perhaps the most enigmatic malignancy in men. If men lived long enough, they would almost all die with histological evidence of the disease being present (Selly et al. 1997). However, only 3% of men die as a consequence of prostate cancer.

This chapter sets out the basic epidemiology of prostate cancer, its relevance to the men in whom it is diagnosed and its impact on health services. The full epidemiology report appears on the CD-ROM that accompanies this guideline.

1.2 Incidence

Prostate cancer is the most common cancer in men and now makes up approximately 25% of the new diagnoses of malignant cancer in men in England and Wales. The incidence appears to be rising (Figure 1.1).

Between 1996 and 2004 the age standardised incidence rate of prostate cancer increased in all cancer networks in England and Wales. In England the average increase was 20% whilst in Wales it was 49%. There was a range of increases in individual networks between 1% and 66%. These increased rates may result from differences in local policy for PSA testing.

\[\text{Figure 1.1} \quad \text{Directly Age Standardised Rate (ASR) of prostate cancer incidence in England and Wales (to European standard population). Data source: Office of National Statistics MB1 series and Welsh Cancer Intelligence unit and Surveillance (WCISU).}\]

\[\text{\textsuperscript{1} Data Source: cancer registries of England and Wales.}\]
From age 50 the incidence increases approximately linearly with age and data indicates that 1% of all men in England and Wales aged 85 or over are diagnosed with prostate cancer each year (Figure 1.2). This increase is largest in the 65–69 age band indicating that the uptake of PSA testing and subsequent diagnosis of cancer is higher than in younger men.

Figure 1.2 Rate of diagnosis of prostate cancer by 5-year age band. Data source: cancer registries of England and Wales.

Since 1996 the proportion of new diagnoses with a total Gleason score of 6 or less has decreased. This is explained by a shift in pathological reporting practice (University of Liverpool, 2003). The proportion of tumours with a Gleason score of 8 or more has remained approximately constant at between 20 and 25% but the proportion of Gleason score 7 tumours is increasing, from less than 20% in 1996 to more than 30% in 2005 (Figure 1.3).

Figure 1.3 Stacked plot of prostate cancer diagnoses broken down by Gleason score (where the score is recorded) for the South West of England. Data source: British Association of Urological Surgeons registry database and South West Public Health Observatory.
There is a higher incidence of prostate cancer in the less socio-economically deprived areas, which is assumed to be due to higher rates of prostate specific antigen (PSA) testing among affluent men.

There is strong evidence to support a higher incidence in men of African or Caribbean origin (GLOBOCAN 2002). There is a significant, 3-fold increase in the incidence of prostate cancer in black men compared to white men irrespective of the country of origin of the black man (Ben-Shlomo et al. 2007).

1.3 Mortality

Prostate cancer accounts for the second highest number of deaths of any male with cancer in England and Wales below only lung cancer. Between 1996 and 2005 it comprised 13% of all cancer deaths in men.

There has been a statistically significant decline in the age standardised mortality rate between 1993 and 2005 (Figure 1.4). However the number of deaths annually has remained roughly stable. This indicates that the declining mortality rate is counteracted by the ageing of the population.

There is no observable effect on the mortality of the large rise in incidence since the year 2000.

Figure 1.4 Directly Age Standardised mortality Rate (to European Standard population) and number of deaths from prostate cancer in England and Wales 1984–2005. Data source: Office of National Statistics.

There is a variation in mortality across cancer networks in England and Wales during the period of decline in national mortality rate, although there is no consistent regional variation.

The majority of men who die of prostate cancer do so at an advanced age when the probability of death from other causes is high. Therefore any treatment that delays their death can plausibly reduce the apparent mortality due to prostate cancer.

Data from the American Surveillance, Epidemiology and End Results (SEER) database (www.seer.cancer.gov/) and the UK PROCESS study (Ben-Schlomo, Personal communication June 2007) show that prostate cancer mortality varies significantly by race. Prostate cancer mortality is higher in black men than white men, driven by the markedly higher incidence. The fatality ratio however is not significantly different.

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1 Data Source: cancer registries of England and Wales.
2 Data Source: Office of National Statistics and Ordnance Survey.
1.4 Survival

In most cases prostate cancer has a long preclinical phase between onset and the appearance of clinical symptoms. The survival time after a symptomatic diagnosis is also long. Therefore the measured survival time for prostate cancer is easily confounded by lead time bias, introduced by bringing forward the point of diagnosis with the extended use of biochemical screening.

Any measure of prostate cancer survival, especially one taken on a population basis, reflects changes in patient prognosis and a lead-time effect due to changes in diagnostic practice. Differences in survival between countries are therefore more likely to be the result of differences in diagnostic practice than the clinically relevant experience of the patient.

1.5 Diagnosis and Investigations

Four procedures are commonly used to diagnose prostate cancer: digital rectal examination (DRE), the PSA blood test, trans-rectal ultrasound (TRUS) and needle biopsy. DRE procedures are not well recorded in any centralised data source.

The level of PSA testing is not centrally monitored in England and Wales. However, several surveys of GP practices and pathology laboratories have been carried out in recent years. There has been a significant increase in the rate of PSA testing from 1999 to 2002 (Melia et al. 2003; Melia et al. 2004). The rate of PSA testing decreased with increasing socio-economic deprivation, and independently decreased with increasing proportion of either black or Asian populations. Approximately 50% of PSA tests are ordered by GPs with a third of these tests being in asymptomatic men.

The number of needle biopsies performed nationally is also not well recorded as they are commonly performed as outpatient procedures and the data may not be reliably captured. An estimate of the number of needle biopsies performed in England and Wales is between 56,000 and 89,000 per year. This is equivalent to 1 million cores needing histological assessment in undiagnosed men.

1.6 Surgery

The primary curative surgical procedure for prostate cancer is the total removal of the prostate, known as prostatectomy. The number of radical prostatectomy operations on men with prostate cancer more than trebled between 1997–98 and 2004–05 (Figure 1.5), with a significant rise in all age groups. The number of operations is rising most quickly in the 60–64 and 65–69 age groups.

![Figure 1.5 Numbers of all radical prostatectomy and orchidectomy operations on prostate cancer patients in England. Prostatectomies defined by OPCS code M61, Orchidectomies are defined by OPCS codes N05 and N06. Data source: HES data provided by NATCanSAT.](image-url)
Metastatic prostate cancer can be treated by the surgical removal of the testes, otherwise known as orchidectomy (Cancer Research UK). This suppresses the level of testosterone in the body and retards the growth of prostate tumours. Surgical orchidectomy is becoming a less common way of treating prostate cancer (see Figure 1.5). From 1997–98 to 2003–04 the number of operations which took place on men with metastatic prostate cancer reduced by 75%. Medical castration, using hormonal therapy, has replaced orchidectomy in most cases.

There is a 4-fold regional variation in the radical prostatectomy rate between cancer networks. After age-standardising the rates of radical prostatectomy, there is still a large variation which confirms that the observed trends are not due to age difference between networks or changes in the age structure of the population.

The majority of prostatectomies recorded on the British Association of Urological Surgeons (BAUS) cancer registry are performed on men with a Gleason score of 6 or 7 (i.e. lower grade tumours)\(^4\). This fraction has remained approximately constant (linear regression shows no significant trend) even while the number of prostatectomies has doubled.

The total number of consultants to which surgical episodes containing either a prostatectomy or cystectomy, in patients diagnosed with prostate or bladder cancer, are registered is approximately constant over the eight years of recorded data. There is a significant drop in the number of consultants with fewer than ten such episodes between 1997–98 and 2004–05, from 86% to 56%. However this is a linear trend with no obvious effect following the publication of the NICE guidance on ‘Improving outcomes in urological cancers’ (NICE 2002). It is therefore likely that the increasing total volume of prostatectomies is driving the reduction in the number of consultants performing a small number of procedures per year. The number of consultants performing these procedures has stayed remarkably consistent, between 371 and 387.

1.7 **Hormonal Therapy**

Hormonal therapy prescriptions have increased dramatically since the mid-1980s\(^5\). Anti-androgen prescriptions rose from zero prior to 1983 to approximately 150,000 per annum in 2004. Prescriptions for luteinising hormone-releasing hormone agonists (LHRH\(a\)) increased from zero prior to 1986 to over 300,000 in 2004. These increases are due to medical castration, using hormonal therapy, replacing orchidectomy in most cases. Oestrogen prescriptions declined between the 1970s and mid 1990s, falling to a minimum of 14,000 prescriptions in 1996 but increased between 1996 and 2004.

Hormonal therapy constitutes the biggest single area of cancer drug spending. The total cost of all prescriptions recorded by the NHSBSA PPD in 2004 was £8.1 billion (Department of Health 2004). Of this £292 million was recorded under BNF section 8, ‘Malignant Disease & Immunosuppression’ with hormone treatment for prostate cancer making up approximately 40%.

1.8 **Radiotherapy**

The large number of radiotherapy procedures carried out on patients with Gleason score 6 and 7 tumours suggests that radical radiotherapy is a more common treatment than prostatectomy\(^6\). Clear differences in the patterns of dose and fractionation occur across NHS trusts, indicating a variation in practice\(^7\).


Following the publication of the NICE guidance on ‘Improving outcomes in urological cancers’ (NICE 2002), a process was put in place in England (as for other cancer sites covered by Service Guidance from the Department of Health or NICE) to monitor the progress made in

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\(^4\) Data source: BAUS cancer registry.

\(^5\) Data Source: IMS Health Medical Data Index, London.

\(^6\) Data Source: South West Public Health Observatory and RES dataset provided by NatCanSAT.

\(^7\) Data Source: RES data provided by NATCanSAT.
implementing the changes in service organisation and delivery which had been recommended. Each cancer network in England and all the designated local and specialist urological cancer teams were reviewed by a team of clinical peers between November 2004 and May 2007.

The findings of these reviews were that the implementation of the guidance was slow and incomplete with almost one third of networks not having compliant action plans for the implementation of the guidance. This was mostly due to the designated specialist urology cancer teams serving populations of less than 1 million. Some networks have still not submitted agreed plans. There was also frequent failure to comply with the key recommendation about surgeons performing fewer than five radical prostatectomies per year.

Local urology cancer teams performed particularly poorly for attendance of core members at multidisciplinary team (MDT) meetings, cover arrangements, referral guidelines, patient experience and service improvement. One quarter of teams did not have complete core membership, most notably for clinical oncology (11%). Oncology attendance at MDT meetings was deficient in 23% of teams. Attendance of radiologists and pathologists was also relatively low.

Overall levels of compliance with the guidance were lower for urology teams than for all other reviewed cancer sites (e.g. breast, colorectal and gynaecology).

The average workload of clinical nurse specialists (CNS) in areas excluding urology is 110 new cases per year per CNS while in Urology it is 203 new cases per year per CNS (Honnor et al. 2006).

Since the key recommendations of the 2002 ‘Improving outcomes in urological cancers’ guidance there has been a rapid increase in the number of patients accrued to clinical trials, which can be attributed mainly to the creation of the NCRI and the NCRN.

References
GLOBOCAN (2002) Data held by the Descriptive Epidemiology Groups of IARC and provided by CANCER Mondial. Available online at www-dep.iarc.fr/.
2 Communication and support

2.1 Introduction

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

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

This previous published guidance from NICE and DH identifies many communication and information needs which apply to men with prostate cancer. There is evidence from the National Audit Office (2005a; 2005b) that these recommendations remain relevant, but have been particularly poorly implemented in this group.

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

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

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

Partners are perceived as the main care-giver and may experience more distress than men with prostate cancer. Partners are thought to be more avid information seekers than men with prostate cancer and while beneficial it is also known to be confusing. Partners are known to be
eager to help in the decision making process, but at the same time this is also known to lead to panic and an inability to search for 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 multi media 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.

**Recommendations**

- The recommendations on communication and patient-centred care made in the two NICE cancer service guidance documents ‘Improving outcomes in urological cancers’ (2002) and ‘Improving supportive and palliative care for adults with cancer’ (2004) should be followed throughout the patient journey.

**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.
Communication and support

Clinical Evidence

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.

Health Economic Evaluation

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 3 for recommendations on nomograms)
- guiding the patient through each step in making a decision, taking into account an individual’s beliefs and values.

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

Recommendations (cont.)

- Men with prostate cancer should be offered 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).
- Men with prostate cancer should be offered advice on how to access information and support from websites (for example, UK Prostate Link www.prostate-link.org.uk), local and national cancer information services, and from cancer support groups.
- Before choosing or recommending information resources for men with prostate cancer, healthcare professionals should check that their content is clear, reliable and up to date. Healthcare professionals should seek feedback from men with prostate cancer and their carers to identify the highest quality information resources.
- Healthcare professionals caring for men with prostate cancer should ascertain the extent to which the man wishes to be involved in decision making and ensure that he has sufficient information to do so.

Qualifying statement: There was GDG consensus in support of these recommendations, based on evidence of unmet need.
Prostate cancer: diagnosis and treatment

Clinical Evidence
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.

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

2.4 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
• Healthcare professionals should 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.

Qualifying statement: This recommendation is based on GDG consensus alone.

Recommendation
• Healthcare professionals should 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.

Qualifying statement: This recommendation is based on GDG consensus alone.

1 A decision aid for men with localised prostate cancer is in development in the UK by the Urology Informed Decision Making Steering Group (publication expected 2008).
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 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

- Healthcare professionals should 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. Healthcare professionals should support men and their partners or carers in making treatment decisions, taking into account the effects on quality of life as well as survival.
- Healthcare professionals should 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

Qualifying statement: These recommendations are based on qualitative evidence and GDG consensus.

Clinical Evidence

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).

Health Economic Evaluation

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.
References


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). This section assumes that men have had a digital rectal examination (DRE) and usually a prostate specific antigen (PSA) test, as set out in the referral guidelines for suspected cancer (NICE clinical guideline 27, 2005). 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.

It has been normal practice that men who are found to have an abnormal serum PSA level should have a prostate biopsy. For example, the UK Prostate Cancer Risk Management Programme (PCRMP) states “if your PSA is definitely raised, a prostate biopsy is required to determine whether cancer is present”. This policy, combined with the waiting time targets from the Department of Health in England (Department of Health, 2002), means that it is common for men to have a prostate biopsy as a matter of course within days of referral with an elevated PSA. The current system allows little time or opportunity for men to be involved in the decision whether or not to have a prostate biopsy. The justification for performing biopsy in men with an abnormal PSA is that they are at high risk of prostate cancer. However, data from the Prostate Cancer Prevention Trial (PCPT) (Thompson et al. 2006) have demonstrated that prostate cancer is also a common finding on biopsy in men with a normal PSA level. The data from this large study provide a strong argument against the use of an arbitrary PSA threshold to select men for prostate biopsy.

The aim of prostate biopsy is not to detect each and every prostate cancer. After all, the PCPT demonstrates that the majority of prostate cancers are in men with a normal PSA level. The aim of prostate biopsy is actually to detect those prostate cancers with the potential for causing harm. It has been estimated that, of asymptomatic men in whom prostate cancer is detected by prostate biopsy following PSA measurement, around 50% (Draisma et al. 2003) 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 high risk, not just of prostate cancer, but of significant prostate cancer. Several large studies have analysed the clinical characteristics associated with the finding of higher grade (usually defined as Gleason score ≥7) prostate cancer on biopsy. Factors significantly associated with high grade cancer were: PSA level, smaller prostate volume, abnormal DRE findings, age, and black African and black Caribbean ethnicity, whereas a previous negative prostate biopsy reduced this risk. These factors have been incorporated into predictive models, based

1 For more information on PSA please see Appendix 1.
on North American data, that allow an individualised assessment of the risk of high grade disease on biopsy. In the above studies, the chance of finding higher grade prostate cancer on biopsy was not related to the presence or absence of lower urinary tract symptoms.

**Recommendations**

- To help men decide whether to have a prostate biopsy, healthcare professionals should 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 and black Caribbean ethnicity) and any history of a previous negative prostate biopsy. The serum PSA level alone should not automatically lead to a prostate biopsy.
- Men and their partners or carers should be given information, support and adequate time to decide whether or not they wish to undergo prostate biopsy. The information should 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.

**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.

**Clinical Evidence**

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.

**Health Economic Evaluation**

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), prostate biopsy for histological confirmation should not be performed, unless this is required as part of a clinical trial.

**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**

No directly relevant studies were identified. Evidence from two case series (Vandecande-laere 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...
Clinical Evidence (cont.)

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.

Health Economic Evaluation

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

The diagnosis of prostate cancer is usually made with ultrasound-guided prostate biopsy. Some men will have a diagnosis confirmed on the tissue obtained at TURP or holmium laser resection of the prostate (HoLeP).

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

The Gleason score of the tumour biopsy and the extent of cancer within the prostate are relevant to the choice of therapy as well as the outcome for the man.

Recommendations

• Healthcare professionals should carry out prostate biopsy following the procedure recommended in ‘Undertaking a transrectal ultrasound guided biopsy of the prostate’ (PCRMP 2006).
• The results of all prostate biopsies should be reviewed by a urological cancer MDT. Men should only be re-biopsied following a negative biopsy after a multidisciplinary team (MDT) review of the risk characteristics including life expectancy, PSA, DRE and prostate volume.
• Men should decide whether or not to have a re-biopsy following a negative biopsy, having had the risks and benefits explained to them.

Qualifying statement: These recommendations, made in the absence of reliable research evidence, are based on GDG consensus.

Clinical Evidence

Observational studies, and theoretical considerations, suggest that re-biopsy will detect prostate cancer in some men with an initially negative prostate biopsy. Six of these studies reported multivariate analyses of predictive factors for positive repeat biopsy (Djavan et al. 2000; Eggener et al. 2005; Fowler, Jr. et al. 2000; Lopez-Corona et al. 2003; Mian et al. 2002; Roobol et al. 2006) but there was disagreement on which factors predict re-biopsy outcome. There is evidence, however, that the odds of high grade prostate cancer are reduced if a man has previously had a negative biopsy.

Health Economic Evaluation

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

The TNM classification (see Appendix 2) 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 pathological 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).

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**

- Healthcare professionals should determine the provisional treatment intent (radical or non-radical) before decisions on imaging are made.
- Imaging is not routinely recommended for men in whom no radical treatment is intended.

**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). The recommendations for imaging are similarly based on these prognostic groups.

- 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 or T2c
- High-risk - PSA > 20 ng/ml, or Gleason score 8-10, or clinical stage T3-T4.

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.

**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 (spread outside the prostate).
Magnetic resonance imaging (MRI) is now the most accurate and commonly used imaging technique for T-staging men with prostate cancer. Many of the original publications used now outdate MRI technology, and the accuracy reported for MRI is improving, typically with endorectal coil imaging at 1.5 Tesla.

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

Magnetic resonance spectroscopy (MRS) is an experimental technique based on the concentration of metabolites such as choline and citrate in the prostate gland. Prostate cancer alters the concentration of these metabolites and this may be used to find areas of tumour activity.

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. Neither technique can characterise the internal architecture of an enlarged node. 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.

For men with low and intermediate risk disease, MRI is commonly used but the evidence supporting this is insubstantial and further research is required.

**Recommendations**

- Computerised tomography (CT) of the pelvis is not recommended for men with low-or intermediate-risk localised prostate cancer.

  **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.

- Men with high-risk localised and locally advanced prostate cancer who are being considered for radical treatment should have pelvic imaging with either magnetic resonance imaging (MRI), or CT if MRI is contraindicated.

  **Qualifying statement:** There is evidence from observational studies to support making this recommendation.

- Magnetic resonance spectroscopy (MRS) is not recommended for men with prostate cancer except in the context of a clinical trial.

  **Qualifying statement:** There is no evidence to support routine use of MRS.

**Clinical Evidence**

No studies measuring the impact of diagnostic imaging on patient outcomes were found; instead most studies were of diagnostic test accuracy.
Clinical Evidence (cont.)

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.

Health Economic Evaluation

The literature review identified 587 potentially relevant papers. Five papers were obtained for appraisal of which one full economic evaluation was subsequently identified (Jager 1994). The evaluation looked at the use of MRI for men with localised prostate cancer for whom radical treatment was intended compared with no MRI, in men with Gleason scores of between 5 and 7.

The economic evaluation was undertaken by building a decision tree, and using the results from a (non-systematic) literature review to identify the necessary information. Expected life years and quality-adjusted life years (QALYs) were used to measure treatment benefits, and the analysis was performed from a US healthcare perspective. The authors made a number of assumptions including the following: MRI was performed in addition to other staging methods in patients considered candidates for radical prostatectomy; and extracapsular disease on MRI contraindicated surgery. However, it should be noted that no randomised studies were identified in which the therapeutic efficacy of MRI staging as a prelude to radical treatment had been assessed, future costs and health benefits were not discounted and no price year was provided.

For the surgical strategy based on clinical staging life expectancy was 12.60 years and the number of QALYs was 12.52. For the MRI strategy the life expectancy was 12.59 and the number of QALYs was 12.53. Thus, the differences in clinical effect were marginal. The total costs amounted to US$11,669 for the surgical strategy based on clinical staging and US$10,568 for the MRI strategy. The incremental cost per life-year gained was approximately US$110,000 if clinical staging alone was used instead of MRI and clinical staging. However, when QALYs were used to measure health outcomes, MRI became the more effective and less costly option. Sensitivity analysis showed that these results were sensitive to a number of assumptions, including the prior probability of extracapsular disease. The authors concluded that the cost-effectiveness of MRI was yet to be established in this patient group, which seems to be a reasonable interpretation of the results.

No further economic analysis was undertaken because it was thought unlikely that subsequent cost-effectiveness estimates would be any more robust given the quality of available clinical information.

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.
Clinical Evidence

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.

Health Economic Evaluation

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

• Isotope bone scans are not routinely recommended for men with low-risk localised prostate cancer.

Qualifying statement: This recommendation is supported by case series evidence and will reduce unnecessary investigation.

Clinical Evidence

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

Health Economic Evaluation

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.

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, and
11-C choline.

**Recommendation**
- PET imaging for prostate cancer is not recommended in routine clinical practice.

**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. Nomo-
grams 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.

**Recommendations**
- 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.

**Qualifying Statement:** There is good quality evidence to support this recommendation.

- When nomograms are used, healthcare professionals should clearly explain the
reliability, validity and limitations of the prediction.

**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**

There is good evidence from observational studies (see evidence review), largely from out-
side the UK, that nomograms can identify risks for men with prostate cancer. Most nomo-
grams have been developed for use in men with clinically localised disease who are candi-
dates 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.

**Health Economic Evaluation**

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 Recommendations

- More research is recommended into the use of MRI in men with intermediate-risk disease (PSA 10–20 ng/ml, or Gleason score 7, or clinical stage T2b or T2c) to inform management decisions.
- More research is recommended into the use of MRS in prostate cancer.

References


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) testing has become common only in the last ten years. PSA testing results in overdetection 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 or T2c
- High-risk - PSA > 20 ng/ml, or Gleason score 8-10, or clinical stage T3-T4 (see Chapter 6 for more information on high-risk localised disease).

Recommendation

- Urological cancer multidisciplinary teams (MDTs) should assign a risk category to all newly diagnosed men with localised prostate cancer.

Qualifying statement: This recommendation is based on evidence from well-designed cohort studies.

1 For more information on PSA please see Appendix 1.
Clinical Evidence
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.

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

4.3 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 but there is evidence that implementation is incomplete (see Chapter 1).

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.

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.
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. 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 risk category to be re-assessed at regular intervals by serial PSA estimations, and trans-rectal ultrasound (TRUS) guided prostate biopsy. Active surveillance is an option for men with low-risk disease who are fit for radical treatment in the event of disease progression.

Recommendation

- Men with localised prostate cancer who have chosen a watchful waiting regimen and who have evidence of significant disease progression (that is, rapidly rising prostate specific antigen (PSA) level or bone pain) should be reviewed by a member of the urological cancer MDT.

Qualifying statement: In the absence of evidence there was GDG consensus that this recommendation would avoid unnecessary investigations.

Recommendations

- Men with low-risk localised prostate cancer who are considered suitable for radical treatment should first be offered active surveillance.

Qualifying statement: There is no reliable evidence of the clinical or cost-effectiveness of radical treatment in this group of men. There was GDG consensus that this recommendation would reduce over-treatment.

- Active surveillance is particularly suitable for a subgroup of men with low-risk localised prostate cancer who have clinical stage T1c, a Gleason score 3+3, a PSA density < 0.15 ng/ml/ml and who have cancer in less than 50% of their total number of biopsy cores with < 10mm of any core involved.

- Active surveillance should be discussed as an option with men who have intermediate-risk localised prostate cancer.

- Active surveillance is not recommended for men with high-risk localised prostate cancer.

Qualifying statement: These recommendations are based on longitudinal studies of the risk of clinical progression or death from prostate cancer. There was GDG consensus that these recommendations would reduce the risk of over-treatment.

- To reduce the sampling error associated with prostate biopsy, men who are candidates for active surveillance should have at least 10 biopsy cores taken.

- Active surveillance should include at least one re-biopsy and may be performed in accordance with the ProSTART protocol.

- Men with localised prostate cancer who have chosen an active surveillance regimen and who have evidence of disease progression (that is, a rise in PSA or adverse findings on biopsy) should be offered radical treatment.

- 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 (see Chapter 2).

Qualifying statement: These recommendations are made on the basis of GDG consensus supported by cohort and observational studies.

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Clinical Evidence

A systematic review (Martin et al. 2006) compared protocols for the active surveillance of men with untreated clinically localised prostate cancer. Five relevant case series with predefined measures of disease progression were included, with 451 men in total. Although three of the series were prospective, only one had median follow-up of more than five years.

The only consensus appeared to be the use of PSA tests and DRE in active surveillance, initially at a frequency of every 3 months and every 6 months thereafter. Some of the protocols involved routine TRUS guided prostate biopsies. The review did not contain any evidence about the use of Magnetic Resonance Imaging (MRI) or Magnetic Resonance Spectroscopy (MRS) in active surveillance. There was no evidence about whether changing the frequency of these tests influences outcomes.

Health Economic Evaluation

The literature search on active surveillance protocols identified 294 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.

Clinical Evidence

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.

Health Economic Evaluation

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.

There is no good quality research comparing any of the following treatments. However, the results of ongoing studies, such as ProtecT (http://www.hta.nhsweb.nhs.uk/project/1230.asp), may provide some evidence in the future. HIFU and cryotherapy have become further options requiring evaluation.

Radical prostatectomy

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 and is uncommon over the age of 70.
External beam radiotherapy

External beam radiotherapy is the commonest 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). There is currently a variety of dose-fractionation regimens in use in England and Wales.

Brachytherapy

Brachytherapy is a form of radiotherapy in which the radiation is given using radioactive sources, either permanently implanted seeds (low dose rate) or temporarily implanted wires (high dose rate) directly into the prostate. Possible side effects include alteration in urinary and bowel function and erectile dysfunction (see section 4.5). Brachytherapy may not be possible in men with an enlarged prostate. Significant obstructive lower urinary tract symptoms are a relative contra-indication.

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.

Recommendations

- Healthcare professionals should offer radical prostatectomy or radical radiotherapy (conformal) to men with intermediate-risk localised prostate cancer.
- Healthcare professionals should offer radical prostatectomy or radical radiotherapy (conformal) to men with high-risk localised prostate cancer where there is a realistic prospect of long-term disease control (see recommendations in Chapter 6).
- Brachytherapy is not recommended for men with high-risk localised prostate cancer.

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 oncologists should use conformal radiotherapy for men with localised prostate cancer, receiving radical external beam radiotherapy.

Qualifying statement: There is evidence from randomised controlled trials that conformal radiotherapy reduces toxicity compared with conventional radiotherapy at similar dose.

- Men undergoing radical external beam radiotherapy for localised prostate cancer should receive a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction.

Qualifying statement: There is evidence from randomised controlled trials to support making this recommendation.

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1 This may also apply to some men with locally advanced prostate cancer.
2 This may also apply to some men with locally advanced prostate cancer.
Prostate cancer: diagnosis and treatment

Clinical Evidence

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.

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.

Recommendations (cont.)

- Adjuvant hormonal therapy is recommended for a minimum of 2 years in men receiving radical radiotherapy for localised prostate cancer who have a Gleason score of ≥ 8.
  
  **Qualifying statement:** There is evidence from several randomised trials to support making this recommendation as well as evidence of cost-effectiveness (see Chapter 6).

- High intensity focused ultrasound (HIFU) and cryotherapy are not recommended for men with localised prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions.
  
  **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.

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5 NICE interventional procedures guidance 130, 230 and 259 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.
Clinical Evidence (cont.)

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).

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.

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.
Health Economic Evaluation (see also Appendix 3)

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. 136 papers were obtained for appraisal and 4 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. 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 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
Health Economic Evaluation (cont.)

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 4.1). 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>
<thead>
<tr>
<th></th>
<th>Cost</th>
<th>LY</th>
<th>QALYs1</th>
<th>QALYs2</th>
</tr>
</thead>
<tbody>
<tr>
<td>WW</td>
<td>£6185</td>
<td>9.69</td>
<td>6.96</td>
<td>6.63</td>
</tr>
<tr>
<td>RP</td>
<td>£10619</td>
<td>10.19</td>
<td>7.52</td>
<td>6.36</td>
</tr>
<tr>
<td>ICER</td>
<td>£8868</td>
<td>£7918</td>
<td>Dominated</td>
<td></td>
</tr>
</tbody>
</table>

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’.

Table 4.1 Baseline incremental cost-effectiveness ratios
Health Economic Evaluation (cont.)

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 (Table 4.2).

Table 4.2 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.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Expected Cost of Treatment</th>
<th>Required QALY Increase(^a)</th>
<th>Equivalent Health Gain In Months(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>External beam</td>
<td>£8288</td>
<td>0.07</td>
<td>1</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>£10992</td>
<td>0.16</td>
<td>2</td>
</tr>
<tr>
<td>HIFU</td>
<td>£12188</td>
<td>0.20</td>
<td>2.4</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>£12630</td>
<td>0.21</td>
<td>2.6</td>
</tr>
<tr>
<td>IMRT</td>
<td>£14688</td>
<td>0.28</td>
<td>3.4</td>
</tr>
</tbody>
</table>

IMRT = intensity modulated radiotherapy; HIFU = high intensity focused ultrasound
\(^a\) Required to achieve a cost per QALY gained of £30,000 compared with watchful waiting.
\(^b\) 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 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-effective 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.
4.5 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 both a specialist surgical oncologist and a specialist clinical oncologist.

**Qualifying statement:** In the absence of any evidence there was GDG consensus that men’s decisions should be informed by site specialist clinicians.

**Rectal Problems after Radiotherapy**

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 stage toxicity in the bowel is an important complication of radiotherapy for prostate cancer.

Radiation-induced injury to the bowel may be functional without underlying anatomical disturbance, and symptoms and signs may well be due to treatable causes or intercurrent pathology. There is an increased risk of rectal cancer after pelvic radiation but faecal occult blood testing is a poor discriminator due to telangiectasis and the emerging National Screening Programme for bowel cancer is inappropriate for these men.

There is a relative lack of research and specialisation by oncologists and gastroenterologists in radiation-induced gastrointestinal (GI) tract injury. In consequence, there is no structured way for patients with GI toxicity to be assessed and potential protective treatments have not been tested adequately in man.

**Recommendations**

- Men presenting with symptoms consistent with radiation-induced enteropathy should be fully investigated (including using flexible sigmoidoscopy) to exclude inflammatory bowel disease or malignancy of the large bowel and to ascertain the nature of the radiation injury. Particular caution should be taken with anterior wall rectal biopsy following brachytherapy because of the risk of fistulation.
- Men treated with radical radiotherapy for prostate cancer should be offered flexible sigmoidoscopy every 5 years.
- Steroid enemas should not be used for treating men with radiation proctopathy.
- The nature and treatment of radiation-induced injury to the gastrointestinal (GI) tract should be included in the training programmes for oncologists and gastroenterologists.

**Qualifying statement:** These recommendations are based on expert opinion and GDG consensus.
Clinical Evidence

Many of the trials were not restricted to prostate cancer but included any patients with any malignancy requiring pelvic EBRT. There was inconsistent evidence for the use of aminosalicylates, sucralfate and misoprostol for the prevention of acute bowel toxicity during pelvic radiotherapy. Other trials reported effective interventions for treatment of acute bowel toxicity but each intervention was only tested in a single trial.

There was no evidence, from fifteen randomised trials in patients receiving pelvic radiotherapy, to support the use of radioprotective agents (see evidence review). Other randomised trials demonstrated clinical effectiveness of loperamide (Sherman et al. 1989), octreotide (Yavuz et al. 2002) and butyrate (Vernia et al. 2000) for acute radiation-induced diarrhoea.

A systematic review of non-surgical interventions for late radiation proctopathy (Denton et al. 2002) identified six randomised trials. Although some of studies reported positive results, the trials were small and each examined a different intervention. There was insufficient evidence, therefore, to recommend any specific intervention.

A systematic review (McGough et al. 2004) concluded there was little evidence to support the use of nutritional interventions for acute or chronic gastrointestinal symptoms.

Due to the lack of good evidence for this question the GDG commissioned an expert position paper (see Appendix B of the evidence review).

Health Economic Evaluation

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

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).

Recommendations

• Prior to treatment, men and their partners should be warned that treatment for prostate cancer will result in an alteration of sexual experience, and may result in loss of sexual function.

Qualifying statement: There is evidence from case series and GDG consensus to support this recommendation.

• Men and their partners should be warned about the potential loss of ejaculation and fertility associated with treatment for prostate cancer. Sperm storage should be offered.

Qualifying statement: There is evidence from case series and strong GDG consensus to support making this recommendation.
Clinical Evidence

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.

Health Economic Evaluation

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

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). Slings are currently under evaluation.
Clinical Evidence

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.
Health Economic Evaluation

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 modeling was attempted because there was considered to be insufficient clinical information on which to base a model.

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 outpatient 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.

Recommendations

- Healthcare professionals should discuss the purpose, duration, frequency and location of follow-up with each man with localised prostate cancer, and if he wishes, his partner or carers.
- Men with prostate cancer should be clearly advised about potential longer term adverse effects and when and how to report them.
- 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.
- PSA levels for all men with prostate cancer who are having radical treatment should be checked 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.
- Routine digital rectal examination (DRE) is not recommended in men with prostate cancer while the PSA remains at baseline levels.
- After at least 2 years, men with a stable PSA and who have had no significant treatment complications, should be offered follow-up outside hospital (for example, in primary care) by telephone or secure electronic communications, unless they are taking part in a clinical trial that requires more formal clinic-based follow-up. Direct access to the urological cancer MDT should be offered and explained.

Qualifying statement: In the absence of reliable evidence, these recommendations are based on GDG consensus.

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7 This may also apply to some men with locally advanced prostate cancer.
Prostate cancer: diagnosis and treatment

Clinical Evidence

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).

Health Economic Evaluation

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 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.
- 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.
- Research into the causes, and clinical trials of prevention and management of radiation-induced enteropathy should be undertaken.
- Further research should be conducted into the timing and effectiveness of treatments for erectile dysfunction after all treatments for prostate cancer.
- Further research is required into the causes, prevention and treatment strategies for urinary incontinence in men with prostate cancer.

References


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) 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 prostate specific antigen (PSA) levels after radical treatment using the same assay technique.

Qualifying statement: There was GDG consensus based on the known variability in assays to make this recommendation.

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 a PSA of > 0.4 ng/ml and rising.

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

1 For more information on PSA please see Appendix 1.
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.

**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**

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 + 1 ng/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).

**Health Economic Evaluation**

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.
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.

Recommendations

- Biopsy of the prostatic bed should not be performed in men with prostate cancer who have had a radical prostatectomy.
- Biopsy of the prostate after radiotherapy should only be performed in men with prostate cancer who are being considered for local salvage therapy in the context of a clinical trial.

Qualifying statement: These recommendations are based on evidence from small case series.

Clinical Evidence

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.

Health Economic Evaluation

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

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:
  - Routine MRI scanning should not be performed prior to salvage radiotherapy in men with prostate cancer
  - Perform an isotope bone scan if symptoms or PSA trends are suggestive of metastases.

Qualifying statement: These recommendations are based on case series evidence and GDG consensus.
Clinical Evidence

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; Mobjideen 2002; Thomas et al. 2003 Nagda et al. 2007).

Health Economic Evaluation

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.

Recommendations

- Biochemical relapse (a rising PSA) alone should not necessarily prompt an immediate change in treatment.
- Biochemical relapse should trigger an estimate of PSA doubling time, based on a minimum of 3 measurements over at least a 6 month period.

Qualifying statement: There is evidence from longitudinal studies and clinical trials to support making these recommendations.

Local Salvage Therapy

For men with biochemical relapse following radical prostatectomy

Surveys of current practice in the UK have shown a large variation 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.
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.

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 such as chemotherapy, bisphosphonates and celecoxib are being investigated in continuing clinical trials.

Recommendation

- Hormonal therapy is not routinely recommended for 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.

Qualifying statement: There is evidence from randomised controlled trials to support this recommendation.

Clinical Evidence

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.

Qualifying statement: There is a range of evidence to support this recommendation.

For example RADICALS (www.ctu.mrc.ac.uk/studies/PR10.asp)
Clinical Evidence (cont.)

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.

Health Economic Evaluation

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.

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.

References

PSA false calls? An analysis of 2030 men treated for prostate cancer with external beam or brachytherapy with or without adjuvant.


Welt, T., Nair, B., MacDonald, R. & Rutks, I. Early versus deferred androgen suppression in the treatment of advanced prostastic cancer [Cochrane review]. 2001 ;(4);
6 Locally advanced prostate cancer

6.1 Introduction

There is no universally agreed definition of locally advanced prostate cancer. It includes a spectrum of disease ranging from men with a tumour that has spread through the capsule of the prostate (pT3a) to those with a large T4 cancer that may be invading the bladder or rectum and has spread to pelvic lymph nodes.

The management of men with ‘localised’ prostate cancer but with a high-risk of extracapsular disease (i.e. Gleason score ≥ 8, or PSA > 20) may also be considered under the heading of locally advanced disease.

6.2 Systemic Therapy

There are two main methods of achieving control of prostate cancer by hormonal manipulation: (i) androgen withdrawal (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 and these are discussed in detail in Chapter 7.

Androgen withdrawal commonly causes hot flushes, loss of sexual drive and weight gain. In addition men may become lethargic and describe loss of drive and energy. In the long term, bone mineral density may decrease with an increase risk of pathological fractures.

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).

For many men with locally advanced prostate cancer, hormonal therapy will be the primary therapy (see Chapter 7 for more information on primary hormonal therapy). Bicalutamide monotherapy is sometimes used as an alternative to LHRHa’s for men with locally advanced disease.

Neoadjuvant Therapy

Hormonal therapy is sometimes given for several months before radical treatment. It can be used before radical radiotherapy to reduce the size of the prostate. This may reduce the side effects of radiotherapy by allowing smaller radiotherapy fields to be used. Hormonal therapy may also increase the cell killing effect of radiotherapy. Hormonal therapy has also been given before surgery in order to downstage the tumour and in an attempt to improve the outcome after radical prostatectomy.

Neoadjuvant androgen withdrawal has been shown to improve disease-free and overall survival in men receiving radical radiotherapy for high-risk localised and locally advanced prostate cancer. The role of neoadjuvant androgen withdrawal for low and intermediate-risk disease treated with modern escalated dose radiotherapy has not been well studied.
Adjuvant Therapy

Hormonal therapy has been used following both surgery and radiotherapy with the intention of improving survival. The duration of hormonal therapy has ranged from 6 months to indefinite. 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.

Clinical Evidence

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.

Adjuvant therapy with radical radiotherapy

Several randomised trials (Kumar et al. 2006) have shown that adjuvant androgen withdrawal improves overall survival in men receiving radical radiotherapy. Sub-group analysis suggests that the survival benefit of adjuvant hormonal therapy is greatest in men with high grade disease. Most of the evidence relates to goserelin given for three years or more, but a single randomised trial (Tyrrel et al. 2005) suggests the survival benefit of adjuvant bicalutamide monotherapy is comparable.

Recommendation

- Neoadjuvant and concurrent luteinising hormone-releasing hormone agonist (LHRHa) therapy is recommended for 3 to 6 months in men receiving radical radiotherapy for locally advanced prostate cancer.

Qualifying statement: There is supporting evidence from several randomised trials to make this recommendation.

Recommendations

- Adjuvant hormonal therapy in addition to radical prostatectomy is not recommended, even in men with margin-positive disease, other than in the context of a clinical trial1.

Qualifying statement: There is evidence from randomised controlled trials of a lack of clinical benefit and significant toxicity to support making this recommendation.

- Adjuvant hormonal therapy is recommended for a minimum of 2 years in men receiving radical radiotherapy for locally advanced prostate cancer who have a Gleason score of ≥ 8.

Qualifying statement: There is evidence from several randomised trials to support making this recommendation as well as evidence of cost-effectiveness.

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1 For example RADICALS (www.ctu.mrc.ac.uk/studies/PR10.asp)
**Health Economic Evaluation**

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 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.

**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. Bisphosphonates are also used in the treatment of age-related osteoporosis and, since osteoporosis is a side effect of androgen withdrawal therapy, bisphosphonates have been studied as a preventive measure in men who are starting long-term hormonal therapy with LHRHa's. Other agents such as cox-2 inhibitors and chemotherapy are being investigated as adjuvant therapy for men with locally advanced prostate cancer.

**Recommendation**

- Bisphosphonates should not be used for the prevention of bone metastases in men with prostate cancer.

**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**

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.
Health Economic Evaluation

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.

6.3 Local Management of Locally Advanced Prostate Cancer

Radiotherapy

The role of radiotherapy in the management of locally advanced prostate cancer is unclear. For those with high-risk locally advanced disease (> 25% risk of lymph node spread (Partin et al. 2001) the value of radiotherapy in addition to hormonal therapy has been studied in a randomised clinical trial (Mason et al. 2000) but the results are not yet available. If radiotherapy is used there are unresolved issues relating to dose, technique and volume.

Treatment to the prostate alone is currently the standard approach to radical radiotherapy for prostate cancer in the UK. In common with other cancer sites (e.g. breast), there may be a benefit from treating regional lymph nodes as well. The best available data on this issue, although immature, are from the RTOG 9413 trial (Lawton et al. 2005).

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. Studies have shown improved survival in men treated with hormonal therapy and radiotherapy compared to historical series treated with hormonal therapy alone, but the improvement may be due to improved staging and case selection.
Clinical Evidence

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.

Health Economic Evaluation

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.

Brachytherapy boost

Brachytherapy can be combined with external beam radiotherapy to deliver a high-dose boost to the prostate in locally advanced disease.

Low dose-rate implant brachytherapy or high dose-rate brachytherapy have been combined with external beam radiotherapy to the low pelvis in those with high-risk localised disease but there are no comparative data.

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 be offered to men with biochemical failure and no evidence of metastatic spread (see Chapter 5).

Recommendation

- Clinical oncologists should consider pelvic radiotherapy in men with locally advanced prostate cancer who have a > 15% risk of pelvic lymph node involvement who are to receive neoadjuvant hormonal therapy and radical radiotherapy.

Qualifying statement: This recommendation is based on evidence from one large, randomised trial.

Clinical Evidence

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.

Recommendation

- Immediate post-operative radiotherapy after radical prostatectomy is not routinely recommended, even in men with margin-positive disease, other than in the context of a clinical trial.

Qualifying statement: There are two randomised trials which have not shown any improvement in survival from immediate post-operative radiotherapy.

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2 Estimated using the Roach formula: %LN risk = 2/3 PSA + (10x [Gleason score - 6])

3 For example RADICALS (www.ctu.mrc.ac.uk/studies/PR10.asp)
Prostate cancer: diagnosis and treatment

**Health Economic Evidence**

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

**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.

**Other Local Therapies**

Cryotherapy or HIFU are used in some centres for men with T2/3 disease as a primary treatment.

**Recommendation**

- High intensity focussed ultrasound (HIFU) and cryotherapy are not recommended for men with locally advanced prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions.

**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.

**Research Recommendations**

- More research should be conducted into the prevention and management of osteoporosis in men receiving long-term withdrawal deprivation therapy.
- The role of radical surgery and extended lymphadenectomy as primary therapy for locally advanced prostate cancer should be studied in clinical trials.

**References**


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4 NICE interventional procedures guidance 130, 230 and 259 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.
Locally advanced prostate cancer

7 Metastatic prostate cancer

7.1 Introduction

This chapter addresses the clinical needs of men with prostate cancer which 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.

7.2 Hormonal Therapy

Androgen withdrawal 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

- Healthcare professionals should offer bilateral orchidectomy to all men with metastatic prostate cancer as an alternative to continuous LHRHa therapy.

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.

7.3 Androgen Withdrawal Versus Combined Androgen Blockade (CAB)

Androgen withdrawal alone is the standard hormonal therapy for metastatic prostate cancer. It has been postulated that the addition of an oral anti-androgen to androgen withdrawal therapy
could improve treatment efficacy and a large number of randomised controlled trials have studied the effect on survival.

### 7.4 Anti-androgen Monotherapy

Anti-androgen monotherapy has been studied in the hope that it would be less toxic than androgen withdrawal but with comparable effectiveness. Several randomised trials have shown that loss of sexual function is less marked with anti-androgen monotherapy than with androgen withdrawal. There is also evidence that anti-androgen monotherapy causes less reduction in bone mineral density (BMD) than androgen withdrawal 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 withdrawal 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.

### Recommendations

- **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, anti-androgen monotherapy with bicalutamide (150 mg)\(^1\) is appropriate.**

  *Qualifying statement:* Evidence from randomised trials confirms the relative protection from loss of sexual function.

- **Healthcare professionals should begin androgen withdrawal and stop bicalutamide treatment in men with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function.**

  *Qualifying statement:* This recommendation is based on GDG consensus alone.

### 7.5 Intermittent Androgen Withdrawal

The standard approach to hormonal therapy has been continuous treatment. Long-term results from uncontrolled studies of intermittent therapy have shown satisfactory outcomes. Several randomised trials are testing whether intermittent therapy might be less toxic, and whether overall survival is unimpaired or even improved. These trials are not yet mature. Intermittent therapy will probably be cheaper than continuous therapy despite the need for closer monitoring.

### Recommendation

- **Intermittent androgen withdrawal may be offered to men with metastatic prostate cancer providing they are informed that there is no long-term evidence of its effectiveness.**

  *Qualifying statement:* This recommendation is based on GDG consensus in the light of the results of uncontrolled studies.

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\(^1\) At the time of publication (February 2008) bicalutamide did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
**Clinical Evidence**

*Orchidectomy versus LHRHa’s*

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.

**Health Economic Evaluation**

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 orchidectomy 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.
Clinical Evidence

LHRHa’s versus CAB

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 withdrawal alone (Prostate Cancer Trialists 2000). Using the rate of treatment withdrawal 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.

Anti-androgen monotherapy

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 withdrawal. The proportion withdrawing from anti-androgen monotherapy and LHRHa treatment was similar, however, suggesting comparable tolerability (Seidenfeld et al. 2000; Seidenfeld et al. 2001).

Intermittent androgen withdrawal

The literature search identified no reliable evidence about the impact of intermittent androgen withdrawal on survival. In their systematic review of five small randomised trials, Conti and co-workers (Conti et al. 2007) concluded that the available information suggests that intermittent androgen deprivation therapy may have a slightly reduced risk of adverse events when compared with continuous androgen deprivation.

7.6 Managing the Complications of Hormonal Therapy

Randomised trials of interventions for complications of hormonal therapy are limited to the management of hot flushes, gynaecomastia and tiredness. Our recommendations are therefore limited to the evidence available.

The interventions for hot flushes that have been studied are diethylstilboestrol, cyproterone acetate, megestrol acetate, clonidine, and oestrogen patches. Since the severity and frequency of hot flushes can improve spontaneously over time, non-randomised studies are of uncertain value. Interventions that have been used for hot flushes, but have not been studied in randomised trials, include selective serotonin reuptake inhibitors (SSRIs), sage, black cohosh and acupuncture.

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.

Recommendations

- Synthetic progestogens (administered orally or parenterally) are recommended as first-line therapy for the management of troublesome hot flushes. If oral therapy is used, it should be given for 2 weeks, and re-started, if effective, on recurrence of symptoms.
- Men starting long-term bicalutamide monotherapy (> 6 months) should receive prophylactic radiotherapy to both breast buds within the first month of treatment. A single fraction of 8 Gy using orthovoltage or electron beam radiotherapy is recommended.
Clinical Evidence

Hot flushes

Placebo controlled randomised trials have demonstrated that diethylstilbestrol (Atala et al. 1992) and megestrol acetate (Loprinzi et al. 1994) are effective in the treatment of hot flushes in men treated with hormonal therapy. Very small randomised trials have shown beneficial results from the use of oestrogen patches (Gerber et al. 2000) and cyproterone acetate (Eaton & McGuire 1983). A small case series (Langenstroer et al. 2005) suggested that intramuscular medroxyprogesterone acetate reduced the frequency and severity of hot flushes.

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.

Health Economic Evaluation

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

7.7 Hormone-Refractory Prostate Cancer

There is no universally accepted definition of hormone refractory disease. The disease can be considered to be hormone refractory when androgen withdrawal 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 refractory disease, so defined, may still respond to agents such as oestrogens or corticosteroids that probably work via the androgen receptor. Even when the disease becomes hormone refractory the androgen receptor on the cancer cells can remain active and LHRHa therapy is usually continued.

There is no known curative therapy for hormone refractory 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-refractory disease, their treatment options should be discussed by the urological cancer multidisciplinary team (MDT) with a view to seeking an oncological and/or specialist palliative care opinion as appropriate.

Qualifying statement: There was GDG consensus that the management of these men is not usually discussed at MDT meetings despite the recommendations in the NICE cancer service guidance ‘Improving outcomes in urological cancers’ (NICE 2002).
7.8 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 chemotherapy regime licensed for use in hormone-refractory 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. Men with poor performance status who may not tolerate docetaxel are usually treated with the combination of mitoxantrone and prednisolone.

Several trials are investigating the use of docetaxel earlier in the course of the disease. It is not clear whether there is a significant benefit from second line treatment with mitoxantrone or newer chemotherapy drugs for men who have failed docetaxel.

New chemotherapy regimens, targeted therapies and cancer vaccines are currently in clinical trial in prostate cancer.

Recommendations (from NICE technology appraisal guidance 101)

- Docetaxel is recommended, within its licensed indications, as a treatment option for men with hormone-refractory metastatic prostate cancer only if their Karnofsky performance-status score is 60% or more.
- 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.
- Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.

Qualifying statement: These recommendations are from ‘Docetaxel for the treatment of hormone-refractory metastatic prostate cancer’, NICE technology appraisal guidance 101 (2006). It has been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

7.9 Oestrogens and Steroids

Diethylstilboestrol is a synthetic oestrogen that can reduce the PSA level in men with hormone refractory 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-refractory prostate cancer. Low dose steroids can reduce the production of adrenal androgens in men on androgen withdrawal 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

- A corticosteroid such as dexamethasone (0.5 mg daily) daily is recommended as third-line hormonal therapy after androgen withdrawal and anti-androgen therapy for men with hormone-refractory prostate.

Qualifying statement: There is evidence from several case series to support this recommendation.
Clinical Evidence
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.

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

7.10 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 is currently developing a clinical guideline on metastatic spinal cord compression which may expand these recommendations.

Clinical Evidence
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).

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

Recommendations
- Men with hormone-refractory prostate cancer shown to have extensive metastases in the spine (for example, on a bone scan) should have spinal MRI if they develop any spinal related symptoms.

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.

- The routine use of spinal MRI for all men with hormone-refractory prostate cancer and known bone metastases is not recommended.

Qualifying statement: There is no evidence to support routine use of MRI in this situation.
7.11 Bone Targeted Therapies

Men with prostate cancer may benefit from bone targeted therapies such as bisphosphonates and Strontium-89, either as treatment for symptomatic bone metastases as a preventive measure to delay or suppress the metastases or as treatment for the osteoporosis caused by hormonal therapy.

Bisphosphonates are also used to treat cancer-related hypercalcaemia.

Androgen withdrawal therapy is a risk factor for the development of osteoporosis.

**Recommendations**

- The use of bisphosphonates to prevent or reduce the complications of bone metastases in men with hormone-refractory prostate cancer is not recommended.

**Qualifying statement:** There is inconsistent evidence, from several RCTs, of the effectiveness of bisphosphonates in preventing or reducing complications of bone metastases.

- Bisphosphonates for pain relief may be considered for men with hormone-refractory prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed. The oral or intravenous route of administration should be chosen according to convenience, tolerability and cost.

**Qualifying statement:** A systematic review supports this recommendation.

**Clinical Evidence**

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.

**Health Economic Evaluation**

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.

**Recommendation**

- Bisphosphonates should not be used routinely to prevent osteoporosis in men with prostate cancer receiving androgen withdrawal therapy.

**Qualifying statement:** This recommendation is based on a lack of evidence that the incidence of bone fractures is reduced.
Clinical Evidence

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).

Health Economic Evaluation

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 fractures.

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.

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 shown encouraging results in early studies in prostate cancer and further studies are planned.

Recommendation

- Strontium-89 should be considered for men with hormone-refractory prostate cancer and painful bone metastases, especially those men who are unlikely to receive myelosuppressive chemotherapy.

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

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 (90Sr-chloride) and samarium-153 (153Sm-EDTMP) are effective for the control of pain from bone 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).
Health Economic Evaluation

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.

7.12 Pelvic Targeted Therapies

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-refractory 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.
Prostate cancer: diagnosis and treatment

Clinical Evidence

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.

Health Economic Evaluation

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

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.

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 aperients and consideration of radiotherapy. Complete obstruction of the lower bowel may require a defunctioning colostomy.

7.13 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.

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.

Recommendations

- Decompression of the upper urinary tract by percutaneous nephrostomy or by insertion of a double J stent should be offered to men with obstructive uropathy secondary to hormone-refractory prostate cancer.
- The option of no intervention should also be discussed with men with obstructive uropathy secondary to hormone-refractory prostate cancer and remains a choice for some.

Qualifying statement: These recommendations are based on observational evidence of effectiveness and GDG consensus.
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.

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.mcpcil.org.uk/liverpool_care_pathway) and the Gold Standards Framework (http://www.goldstandardsframework.nhs.uk/) are models that facilitate the quality of care at the end of life.

Recommendations

- Men with metastatic prostate cancer should be offered tailored information and access to specialist urology and palliative care teams to address the specific needs of men with metastatic cancer. They should have the opportunity to discuss any significant changes in their disease status or symptoms as these occur.
- The regular assessment of needs should be applied systematically to men with metastatic prostate cancer².
- Palliative interventions at any stage should be integrated into coordinated care, and any transitions between care settings should be facilitated as smoothly as possible.
- Healthcare professionals should discuss personal preferences for palliative care as early as possible with men with metastatic prostate cancer, their partners and carers. Treatment/care plans should be tailored accordingly and the preferred place of care should be identified.
- Healthcare professionals should 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.

Qualifying statement: There is evidence from qualitative studies and GDG consensus to support these recommendations.

Clinical Evidence

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).

Health Economic Evaluation

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 clinical trials should be conducted to determine if there is a role for bisphosphonates in men with prostate cancer.

References


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.


Appendix 1

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.

References


# Appendix 2

## TNM Staging for Prostate Cancer

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SUB-STAGE</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td></td>
<td><strong>Clinically unapparent tumour, not detected by digital rectal examination nor visible by imaging</strong></td>
</tr>
<tr>
<td></td>
<td>T1a</td>
<td>Incidental histological finding; ≤5% of tissue resected during TURP</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>Incidental histological finding; &gt;5% of tissue resected during TURP</td>
</tr>
<tr>
<td></td>
<td>T1c</td>
<td>Tumour identified by needle biopsy</td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td><strong>Confined within the prostate</strong></td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>Tumour involves half of the lobe or less</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>Tumour involves more than one half of one lobe but not both lobes</td>
</tr>
<tr>
<td></td>
<td>T2c</td>
<td>Tumour involves both lobes</td>
</tr>
<tr>
<td>T3</td>
<td></td>
<td><strong>Tumour extends through the prostate capsule but has not spread to other organs</strong></td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>Extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td></td>
<td>T3b</td>
<td>Tumour invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td></td>
<td><strong>Tumour is fixed or invades adjacent structures other than seminal vesicles</strong></td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>Tumour invades bladder neck and/or external sphincter and/or rectum</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Tumour invades levator muscles and/or is fixed to pelvic wall</td>
</tr>
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### Node

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<tr>
<td>Node</td>
<td></td>
<td><strong>Regional lymph nodes</strong></td>
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<tr>
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<td>NX</td>
<td>Regional lymph nodes can not be assessed</td>
</tr>
<tr>
<td></td>
<td>N0</td>
<td>No regional lymph nodes metastasis</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>Regional lymph node metastasis</td>
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### Metastasis

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<th>DEFINITION</th>
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</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>MX</td>
<td>Distant metastasis can not be assessed</td>
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<tr>
<td></td>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1a</td>
<td>Non-regional lymph node(s)</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td>Bone(s)</td>
</tr>
<tr>
<td></td>
<td>M1c</td>
<td>Metastasis at other site(s)</td>
</tr>
</tbody>
</table>

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Appendix 3

An Economic Evaluation of Radical Prostatectomy Versus Alternative Treatment Options for Clinically Localised Prostate Cancer

Introduction

The aim of this study was to assess the cost-effectiveness of a number of different treatment options for clinically localised prostate cancer.

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. 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.

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.
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 (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).

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.

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 A3.1). 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 A3.1 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).

**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\(^3\) from the published 10-year Kaplan-Meier disease-specific survival curve (Figure A3.2). 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.

![Figure A3.2](image-url) 

*Figure A3.2* Reported and extrapolated disease-specific survival curves and hazard functions derived from Bill-Axelson et al. (2005).

RP, Radical Prostatectomy; WW, Watchful Waiting

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\(^{2}\) The latter scenario was taken to represent the main baseline result.

\(^{3}\) 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.
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 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 A3.1) 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.

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 value of 0.78. 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).

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4 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.

5 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.

6 Cowen et al. (1999) derived these values in 31 individuals using the time-trade-off method.
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).

**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 A3.1). 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.

**Table A3.1 Unit cost estimates.**

<table>
<thead>
<tr>
<th>Cost</th>
<th>Estimate</th>
<th>Source</th>
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<tbody>
<tr>
<td>Radical Prostatectomy</td>
<td>£5603</td>
<td>Calvert et al. (2003)</td>
</tr>
<tr>
<td>Hormonal Therapy (annual)</td>
<td>£2612</td>
<td>Hummel et al. (2003)</td>
</tr>
<tr>
<td>Transurethral Resection (elective)</td>
<td>£2009</td>
<td>NHS Unit Costs a</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>£115 (per annum)</td>
<td>Turner et al. b</td>
</tr>
<tr>
<td>Twice yearly PSA test</td>
<td>£154</td>
<td>Calvert et al. (2003)</td>
</tr>
<tr>
<td>External Beam Radiotherapy (30 fractions)</td>
<td>£3600</td>
<td>NHS Unit Costs (@ £120 per fraction)</td>
</tr>
<tr>
<td>Two Phase Intensity Modulated Radiotherapy</td>
<td>£10000</td>
<td>Assumption</td>
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<tr>
<td>Brachytherapy</td>
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<td>Hummel et al. (2003)</td>
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<tr>
<td>Cryotherapy</td>
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<td>Hummel et al. (2003)</td>
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<td>HIFU</td>
<td>£7500</td>
<td>EDAP-TMS – quoted in comments on consultation draft</td>
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</table>

aOne-off cost
bThese 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.

**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).
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 compared 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. 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.

Results

The baseline results are shown in Table A3.2. 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 A3.2 Baseline incremental cost-effectiveness ratios.

<table>
<thead>
<tr>
<th></th>
<th>Cost</th>
<th>LY</th>
<th>QALYs1</th>
<th>QALYs2</th>
</tr>
</thead>
<tbody>
<tr>
<td>WW</td>
<td>£6185</td>
<td>9.69</td>
<td>6.96</td>
<td>6.63</td>
</tr>
<tr>
<td>RP</td>
<td>£10619</td>
<td>10.19</td>
<td>7.52</td>
<td>6.36</td>
</tr>
<tr>
<td>ICER</td>
<td>£8868</td>
<td></td>
<td>£7918</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

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’.

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.

7 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.
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-refractory prostate cancer. However, as a proxy, a threshold analysis was undertaken to demonstrate how costly treatment for hormone-refractory 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.

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 A3.3). For example, external beam radiotherapy cost an additional £2103 than watchful waiting.

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*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.*
Prostate cancer: diagnosis and treatment

(£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.

Table A3.3 Results from the threshold analysis over a 20 year period compared to watchful waiting.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Expected Cost of Treatment</th>
<th>Required QALY Increase</th>
<th>Equivalent Health Gain In Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>External beam</td>
<td>£8288</td>
<td>0.07</td>
<td>1</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>£10992</td>
<td>0.16</td>
<td>2</td>
</tr>
<tr>
<td>HIFU</td>
<td>£12188</td>
<td>0.20</td>
<td>2.4</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>£12630</td>
<td>0.21</td>
<td>2.6</td>
</tr>
<tr>
<td>IMRT</td>
<td>£14688</td>
<td>0.28</td>
<td>3.4</td>
</tr>
</tbody>
</table>

aRequired to achieve a cost per QALY gained of £30,000 compared with Watchful Waiting.

bFor 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.

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 (it is anticipated that the ongoing MAPS study will provide more information in these issues https://www.charttrials.abdn.ac.uk/maps/faq.php as will the ProtecT study http://www.hta.nhsweb.nhs.uk/project/1230.asp).

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.

References


Appendix 4

Abbreviations

ACTH  adrenocorticotropic hormone
BPH  benign prostatic hyperplasia
CAB  combined androgen blockade
CNS  clinical nurse specialist
CT  computed tomography
DH  Department of Health
DRE  digital rectal examination
EBRT  external beam radiotherapy
GDG  guideline development group
GI  gastrointestinal
HIFU  high intensity focused ultrasound
HRQoL  health related quality of life
ICER  incremental cost effectiveness ratio
IMRT  intensity modulated radiotherapy
LHRHa  luteinising hormone-releasing hormone agonists
MDT  multi-disciplinary team
MRI  magnetic resonance imaging
MRS  magnetic resonance spectroscopy
NCC-C  National Collaborating Centre for Cancer
NCRI  National Cancer Research Institute
NCRN  National Cancer Research Network
NICE  National Institute for Health and Clinical Excellence
PCPT  Prostate Cancer Prevention Trial
PCRMP  Prostate Cancer Risk Management Programme
PDE5  phosphodiesterase type 5
PET  positron emission tomography
PME  pelvic floor muscle exercise
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>prostate specific antigen</td>
</tr>
<tr>
<td>PSA-DT</td>
<td>prostate specific antigen doubling time</td>
</tr>
<tr>
<td>QALY</td>
<td>quality adjusted life years</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>SRE</td>
<td>skeletal related event</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TRUS</td>
<td>trans-rectal ultrasound</td>
</tr>
<tr>
<td>TURP</td>
<td>trans-urethral resection of the prostate</td>
</tr>
</tbody>
</table>
Appendix 5
Glossary

Active surveillance
A method of managing men with low or intermediate-risk localised prostate cancer that aims to target radical treatment only to those who would benefit most.

Adjuvant treatment
A treatment given in addition to the main treatment.

Androgens
A family of hormones that promote the development and maintenance of male sex characteristics.

Androgen withdrawal
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.

Biopsy
Removal of a sample of tissue from the body to assist in diagnosis of a disease.

Bisphosphonates
A type of cytotoxic drug used to treat bone metastases.
Bone scan
A scan intended to show any abnormal areas of bone.

Bowel toxicity
Symptoms caused by treatment-related damage to the bowel.

Brachytherapy
A form of radiotherapy in which the radiation is given using radioactive sources as either permanently implanted seeds (low dose rate) or temporarily implanted wires (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.

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)
A type of prostate cancer hormone therapy which combines an anti-androgen with either chemical castration or surgical castration.

Comorbidity
The effect of all other diseases an individual patient might have other than the primary disease of interest.

Computed tomography (CT)
An x-ray imaging technique. In spiral CT the x-ray machine scans the body in a spiral path. Also known as helical CT.

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 doctor 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 area surrounding the rectum.

Enteropathy
Disease of the intestines.

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 tissue obtained by prostate biopsy, 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
The presence of blood in the urine. Macroscopic haematuria is visible to the naked eye, and microscopic haematuria is only seen by microscopic examination of a sample from a urine test.

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.

Holmium laser resection of the prostate (HoLeP)
Surgery to remove tissue from the prostate using an instrument inserted via the urethra using a high powered laser. Can be used to improve symptoms in men with restriction to their urinary stream from BPH or a prostate tumour.

Hormonal therapy
Treatment of cancer by removing and/or, blocking the effects of hormones which stimulate the growth of prostate cancer cells.

Hormone refractory (also known as hormone resistant)
A condition where the tumour no longer responds to hormonal 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.

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
Cancer which has been staged as T3 or T4 (spread outside the prostate gland).

Local treatment
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 which allows the form and metabolism of tissues and organs to be visualised (also known as nuclear magnetic resonance).

Magnetic resonance spectroscopy imaging (MRS)
A noninvasive 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 tumor (spacial information).

Maximum androgen blockade
The combined use of LHRHa’s and anti-androgen treatment.

Medical castration
Hormonal therapy with an LHRHa given to lower the levels of the testosterone hormone made by the testicles.

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 number of deaths per unit of population in any specific region, age group, disease or other classification, 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 tumors 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 or surgical castration)
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 test
A test which measures PSA levels in the blood.

PSA velocity
The rate of change of PSA level over time.

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. Conventional external beam radiotherapy also affects some normal tissue outside the target area. Conformal radiotherapy aims to reduce the amount of normal tissue that is irradiated by shaping the x-ray beam more precisely. The beam can be altered by placing metal blocks in its path or by using a device called a multi-leaf collimator. This consists of a number of layers of metal sheets which are attached to the radiotherapy machine; each layer can be adjusted to alter the shape and intensity of the beam.

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.
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 re-occurred 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.

Surgical castration
Treatment which removes the testicles (orchidectomy) and reduces the level of testosterone.

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
A method of managing men with prostate cancer who are not suitable for radical treatment, involving treatment only if and when they develop symptoms.
Appendix 6
Guideline Scope

Guideline title
Prostate cancer: diagnosis and treatment

Short title
Prostate cancer

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 Appendix). 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.

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 Wales1,2 and 9161 deaths3. 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

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2 Welsh Cancer Intelligence and Surveillance Unit, 2003.
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.

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 Appendix).

The areas that will be addressed by the guideline are described in the following sections.

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 diagnosis 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 carcinoma and rhabdomyosarcoma.

Healthcare setting

- Primary care – excluding population-based and opportunistic screening.
- Secondary care.
- Tertiary care by specialist urological cancer teams.

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.

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


Guideline

The development of the guideline recommendations will begin in November 2005.

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.
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 diagnostic and staging procedures – excluding screening
• the main treatment modalities including hormonal treatments (covering surgical and chemical castration)
• the role of tumour specific bisphosphonates.’
Appendix 7

List of Topics Covered by Each Chapter

Chapter 2 – Communication and Support

- How effective are decision aids at informing men with prostate cancer (and their wives/partners/carers/family) about treatment options?
- What are the communication methods that effectively inform men with prostate cancer (and their wives/partners/carers/family) about treatment options?
- What are the perspectives of men who have prostate cancer (and their wives/partners/carers/family) with regard to information/communication needs about treatment options, decision making processes and influencing factors?
- What is the most effective intervention for men with prostate cancer who experience emotional distress caused by loss of masculinity?

Chapter 3 – Diagnosis and Staging of Prostate Cancer

- In men presenting with bone metastases and unknown primary cancer, at what level of prostate specific antigen (PSA) does a biopsy become unnecessary?
- How do we optimise the detection of men with prostate cancer in those men where cancer has been missed on initial investigation, whilst sparing those who do not have cancer from unnecessary repeat investigation or prolonged follow-up?
- In men with clinically localised prostate cancer, for whom radical (curative) treatment is intended, does radiological imaging help to inform the choice of radical treatment? If so which imaging modalities are clinically and cost effective?
- Is there a need for radiological imaging in men with prostate cancer who are not intended for curative treatment?
- In men with localised prostate cancer, what is the validity of published prostate cancer nomograms?
- Should men with suspected prostate cancer who have a raised PSA level automatically be referred for biopsy to determine if they have prostate cancer?

Chapter 4 – Localised Prostate Cancer

- In men with localised prostate cancer what are the risk factors for:
  - Disease specific mortality
  - Lymph node involvement
  - Treatment failure (disease recurrence, biochemical relapse)?
- In men with localised or locally advanced prostate cancer, which treatments (radical prostatectomy, external beam radiotherapy, brachytherapy, conformal radiotherapy, conventional radiotherapy, high intensity focused ultrasound, cryotherapy) are clinically and cost effective compared to watchful waiting?
- In men with prostate cancer, who is eligible to receive active surveillance and what is the most effective protocol to follow?
• In men with prostate cancer receiving active surveillance, what are the indicators for inter-
vention with radical treatment?
• In men with prostate cancer, what are the effective interventions for sexual dysfunction
(either caused by radical treatment or the disease itself)?
• In men who have been treated with radical surgery or radical radiotherapy for prostate
cancer, what are the effective interventions for incontinence?
• In men who have been treated with radical radiotherapy for prostate cancer what are the
effective interventions for radiation toxicity?
• In men who have received treatment for prostate cancer, what is the most effective follow-up
protocol?

Chapter 5 – The Management of Relapse After Radical Treatment

• In men who have had radical treatment for prostate cancer, what is the clinical importance
of biochemical relapse after radical treatment and how should biochemical relapse be
defined?
• In men with biochemical relapse following radical treatment for prostate cancer, what
staging investigations are effective?
• In men with biochemical relapse following radical treatment for prostate cancer, what
salvage therapies for local recurrence are effective?

Chapter 6 – Locally Advanced Prostate Cancer

• In men with prostate cancer does the addition of adjuvant therapy to radical treatment
improve outcomes?
• In men with prostate cancer receiving hormonal therapy, are bisphosphonates effective at
preventing bone metastases?
• What is the clinical and cost-effectiveness of pelvic radiotherapy in patients receiving radical
radiotherapy for prostate cancer?

Chapter 7 – Metastatic Prostate Cancer

• In men with metastatic prostate cancer which type of initial hormonal therapy is clinically
effective?
• In men who have been treated with hormonal therapy for prostate cancer, what are the
effective interventions for managing the complications of hormonal therapy?
• Docetaxel for the treatment of hormone-refractory metastatic prostate cancer, (taken from
the NICE technology appraisal guidance 101 (2006)).
• What is the most effective corticosteroid for the treatment of men with castration refractory
prostate cancer?
• In patients with known bone metastases and no symptoms or signs of spinal cord compres-
sion, does routine MRI scan of the spine at the time of diagnosis of bone metastases improve
outcome?
• In men with prostate cancer can bisphosphonates reduce the risk of bone complications
from androgen deprivation?
• In men with hormone refractory prostate cancer and confirmed bone metastases, can
bisphosphonates delay or improve the complications of bone metastases?
• In patients with hormone refractory prostate cancer with bone metastases, does the addition
of Strontium 89 to standard care improve outcomes?
• What is the most effective management of obstructive uropathy in men with hormone refrac-
tory prostate cancer?
• What is the most effective delivery of palliative care for men with prostate cancer?
Appendix 8

People and Organisations Involved in Production of the Guideline

8.1 Members of the Guideline Development Group
8.2 Organisations invited to comment on guideline development
8.3 Individuals carrying out literature reviews and complementary work
8.4 Expert advisers to the Guideline Development Group
8.5 Members of the Guideline Review Panel
Appendix 8.1

Members of the Guideline Development Group (GDG)

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, Weston 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
## Declaration of Interests

The Guideline Development Group were asked to declare any possible conflicts of interest which could interfere with their work on the guideline.

<table>
<thead>
<tr>
<th>GDG Member</th>
<th>Interest Declared</th>
<th>Type of Interest</th>
<th>Decisions Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark Baker (Chair)</td>
<td>Consultancy work for Roche on high-level Dept of Health policy on cancer about unrestricted grants</td>
<td>Personal pecuniary, non-specific</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Attended several advisory boards for Pharmion on thalidomide</td>
<td>Personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the advisory board was on an intervention that is not used in prostate cancer.</td>
</tr>
<tr>
<td></td>
<td>Consultancy work for Pfizer on high-level Dept of Health policy on cancer about unrestricted grants</td>
<td>Personal pecuniary, non-specific</td>
<td>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.</td>
</tr>
<tr>
<td>John Graham (Lead Clinician)</td>
<td>Received fee from Speciality European Pharma for advisory work on aberalix in prostate cancer</td>
<td>Personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as this interventions is not being investigated by the guideline.</td>
</tr>
<tr>
<td></td>
<td>Received travel, accommodation and expenses from Bayer Pharmaceuticals for attending an ECCO meeting in Paris</td>
<td>Personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.</td>
</tr>
<tr>
<td></td>
<td>Received £500 honorarium + travel expenses from Sanofi-Aventis for giving an invited lecture to the NW Uro-Oncology Group</td>
<td>Personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the lecture was not specific to prostate cancer.</td>
</tr>
<tr>
<td></td>
<td>Received travel and meeting expenses from Astra Zeneca for attending the ASCO Prostate Cancer Symposium in Feb 2006</td>
<td>Personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.</td>
</tr>
<tr>
<td></td>
<td>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)</td>
<td>Non-personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the interventions included in the trial are not being investigated by the guideline.</td>
</tr>
<tr>
<td></td>
<td>Principal Investigator for a trial on circulating tumour cell assay in men with HRPC receiving chemotherapy (Immunicon)</td>
<td>Non-personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the interventions included in the trial are not being investigated by the guideline.</td>
</tr>
<tr>
<td>GDG Member</td>
<td>Interest Declared</td>
<td>Type of Interest</td>
<td>Decisions Taken</td>
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</tr>
<tr>
<td>Chief Investigator for UK in trial of GVAX (immunotherapy) vs docetaxel in HRPC (Cell Genesys)</td>
<td>Non-personal pecuniary, specific</td>
<td>Declare and must withdraw from discussions on all topics that include docetaxel or GVAX as interventions.</td>
<td></td>
</tr>
<tr>
<td>Chief Investigator for UK in trial of docetaxel vs LHRHa vs combination following radical prostatectomy (Sanofi Aventis)</td>
<td>Non-personal pecuniary, specific</td>
<td>Declare and must withdraw from discussions on all topics that include docetaxel. Chairperson’s action to be involved in discussions on LHRHa.</td>
<td></td>
</tr>
<tr>
<td>Principal Investigator for a trial on satraplatin + prednisolone vs prednisolone alone in patients with HRPC (GPC Biotech)</td>
<td>Non-personal pecuniary, specific</td>
<td>Declare and can participate in discussions on all topics as the Principal Investigator does not have supervisory responsibility for the work being undertaken.</td>
<td></td>
</tr>
<tr>
<td>Trial set up meeting for alpharadin in metastatic prostate cancer (Fulcrum Pharma)</td>
<td>Non-personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the interventions included in the trial are not being investigated by the guideline.</td>
<td></td>
</tr>
<tr>
<td>Principal Investigator for trial of S-8184 in transitional cell carcinoma of urothelium (Sonus Pharmaceuticals)</td>
<td>Non-personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the trials are not specific to prostate cancer.</td>
<td></td>
</tr>
<tr>
<td>Principal Investigator for a trial of VEG 102616 in metastatic renal cancer (GlaxoSmithKline)</td>
<td>Non-personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the trials are not specific to prostate cancer.</td>
<td></td>
</tr>
<tr>
<td>Chief Investigator for UK for a trial of Sorafenib in metastatic renal cancer (Bayer Pharmaceuticals)</td>
<td>Non-personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the trials are not specific to prostate cancer.</td>
<td></td>
</tr>
<tr>
<td>Received honorarium from Roche for attending an advisory board on bevacizumab in renal cancer</td>
<td>Personal pecuniary non-specific</td>
<td>Declare and can participate in discussions on all topics as the advisory board was not specific to prostate cancer.</td>
<td></td>
</tr>
<tr>
<td>Philip Barnard</td>
<td>Trustee of the Prostate Cancer Support Association</td>
<td>Personal non-pecuniary</td>
<td>Declare and can participate in discussions on all topics.</td>
</tr>
<tr>
<td>Angela Billington</td>
<td>Received honorarium from Pfizer for giving presentation on overactive bladder syndrome at the Sense of Leadership meeting in June 2007</td>
<td>Personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the presentation given was not specific to prostate cancer.</td>
</tr>
<tr>
<td></td>
<td>Received honorarium from Coloplast for giving presentations on over-active bladder symptoms and catheterisation at nurse training days</td>
<td>Personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the presentation given was not specific to prostate cancer.</td>
</tr>
<tr>
<td>GDG Member</td>
<td>Interest Declared</td>
<td>Type of Interest</td>
<td>Decisions Taken</td>
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<tr>
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</tr>
<tr>
<td>Brendan Carey</td>
<td>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</td>
<td>Non-personal pecuniary, specific</td>
<td>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.</td>
</tr>
<tr>
<td>David Gillatt</td>
<td>Received educational and research grants from Astra Zeneca</td>
<td>Non-personal pecuniary, specific</td>
<td>Declare and must withdraw from discussions on all topics that include interventions made by Astra Zeneca and used in prostate cancer (i.e. bicalutamide &amp; goserelin acetate).</td>
</tr>
<tr>
<td></td>
<td>Received sponsorship from Sanofi Aventis for travel, attendance and expenses to the European Society of Urological Oncology meeting</td>
<td>Personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.</td>
</tr>
<tr>
<td></td>
<td>Observed and had training on the Ablatherm HIFU machine. Expenses reimbursed by EDAP</td>
<td>Personal pecuniary, specific</td>
<td>Declare and must withdraw from discussions of any topics that include HIFU as an intervention&lt;sup&gt;1&lt;/sup&gt;.</td>
</tr>
<tr>
<td></td>
<td>Received honorarium from Succinct Comms for attending an advisory board on docetaxel</td>
<td>Personal pecuniary, specific</td>
<td>Declare and must withdraw from discussions on all topics that include docetaxel&lt;sup&gt;1&lt;/sup&gt; as an intervention.</td>
</tr>
<tr>
<td>Chris Parker</td>
<td>Received a fee from Algeta for speaking at a meeting</td>
<td>Personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as there are no interventions made by Algeta being investigated by the guideline.</td>
</tr>
<tr>
<td></td>
<td>Received honorarium from Sanofi Aventis for giving educational talks on the role of docetaxel in HRPC</td>
<td>Personal pecuniary, specific</td>
<td>Declare and must withdraw from discussions on all topics that include docetaxel&lt;sup&gt;1&lt;/sup&gt; as an intervention.</td>
</tr>
<tr>
<td>GDG Member</td>
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</tr>
<tr>
<td></td>
<td>Received honorarium from Cell Genesys for attending an advisory board on the G0034 trial (docetaxel +/- GVAX)</td>
<td>Personal pecuniary, specific</td>
<td>Declare and must withdraw from discussions on all topics that include docetaxel(^1) or GVAX(^2) as interventions.</td>
</tr>
<tr>
<td></td>
<td>Consultancy work for Algeta</td>
<td>Personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as there are no interventions made by Algeta being investigated by the guideline.</td>
</tr>
<tr>
<td></td>
<td>Principal investigator for a cohort study on active surveillance</td>
<td>Personal non-pecuniary</td>
<td>Declare and can participate in all discussions as neither he nor his department receive any money for this.</td>
</tr>
<tr>
<td></td>
<td>Chief investigator for MRC RADICALS trial which is studying the role of radiotherapy after surgery in prostate cancer</td>
<td>Personal non-pecuniary</td>
<td>Declare and can participate in all discussions as neither he nor his department receive any money for this.</td>
</tr>
<tr>
<td>John Wiles</td>
<td>Chairman and Executive Committee member of the Association for Palliative Medicine of GB &amp; Ireland</td>
<td>Personal non-pecuniary</td>
<td>Declare and can participate in discussions on all topics.</td>
</tr>
<tr>
<td></td>
<td>Medical Director Harris HospisCare</td>
<td>Personal non-pecuniary</td>
<td>Declare and can participate in discussions on all topics.</td>
</tr>
<tr>
<td></td>
<td>Trustee of the National Council for Palliative Care</td>
<td>Personal non-pecuniary</td>
<td>Declare and can participate in discussions on all topics.</td>
</tr>
<tr>
<td></td>
<td>Trustee and Company Director of the Care Not Killing Alliance</td>
<td>Personal non-pecuniary</td>
<td>Declare and can participate in discussions on all topics.</td>
</tr>
<tr>
<td>Jerviose Andreyev (Expert Advisor on radiation toxicity)</td>
<td>Educational grant from Norgine to run an ongoing study into the optimal treatment of radiotherapy-induced faecal incontinence</td>
<td>Non-personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the trials are not specific to prostate cancer.</td>
</tr>
<tr>
<td></td>
<td>Educational grant from SHS International to run a study on the use of elemental diet in preventing acute and long term toxicity</td>
<td>Non-personal pecuniary, non-specific</td>
<td>Declare and can participate in discussions on all topics as the trials are not specific to prostate cancer.</td>
</tr>
</tbody>
</table>

\(^1\) 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.

\(^2\) GVAX was not included as an intervention in any of the topics investigated by the guideline and was therefore not discussed by the GDG.

\(^3\) The recommendations on HIFU had already been drafted by the time this interest occurred so a conflict does not exist.
Appendix 8.2

Organisations Invited to Comment on 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)  
Addenbrooke’s NHS Trust  
Afiya Trust, The  
Age Concern England  
Aintree Hospitals NHS Trust  
Airedale General Hospital  
Albyn Medical Ltd  
American Medical Systems UK  
Amgen UK Ltd  
Anglesey Local Health Board  
Ashfield and Mansfield District PCT  
Association for Continence Advice (ACA)  
Association of Chartered Physiotherapists in Women’s Health  
Association of Clinical Biochemistry  
Association of the British Pharmaceuticals Industry (ABPI)  
Astellas Pharma Ltd  
AstraZeneca UK Ltd  
Aventis Pharma  
Bard Ltd  
Barnsley Acute Trust  
Barnsley PCT  
Bath and North East Somerset PCT  
Bedfordshire & Hertfordshire NHS Strategic Health Authority  
Birmingham Heartlands & Solihull NHS Trust  
Blaenau Gwent Local Health Board  
Boehringer Ingelheim Ltd  
Bostwick Laboratories  
Bradford & Airedale PCT  
Bradford South & West PCT  
British Association for Counselling and Psychotherapy  
British Association of Art Therapists  
British Association of Urological Nurses  
British Association of Urological Surgeons  
British Dietetic Association  
British Geriatrics Society  
British Lymphology Society  
British National Formulary (BNF)  
British Nuclear Medicine Society  
British Oncology Pharmacy Association  
British Prostate Group  
British Psychological Society  
British Uro-oncology Group  
Bromley PCT  
BUPA  
Cancer Black Care  
Cancer Network Pharmacists Forum  
Cancer Research UK
North Sheffield PCT
North Trent Cancer network
Northwest London Hospitals NHS Trust
Novartis Pharmaceuticals UK Ltd
Nucletron B.V.
Nutrition Society
Oncura International
Ortho Biotech
Oxford Nutrition Ltd
Ovarian Cancer Action
PCaSO Prostate Cancer Network
PERIGON (formerly the NHS Modernisation Agency)
Pharmion Ltd
Pierre Fabre Ltd
Primary Care Pharmacists’ Association
Princess Alexandra Hospital NHS Trust
Prostate Brachytherapy Advisory Group
Prostate Cancer Charity, The
Prostate Cancer Research Foundation, The
PSA Prostate Cancer Support Association
Prostate Support Federation
Pfizer Ltd
Queen Victoria Hospital NHS Foundation Trust
Regional Public Health Group - London
Roche Diagnostics Ltd
Roche Products Ltd
Rotherham PCT
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners Wales
Royal College of Nursing (RCN)
Royal College of Pathologists
Royal College of Physicians of London
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal Society of Medicine
Royal West Sussex Trust, The Royal United Hospital Bath NHS Trust Salford PCT
Sandwell PCT
Sanofi-Synthelabo
Schering Health Care Ltd
Scottish Intercollegiate Guidelines Network (SIGN)
Serono Ltd
Sheffield South West PCT
Sheffield Teaching Hospitals NHS Trust
Shropshire County and Telford & Welkin PCT
Siemens Medical Solutions Diagnostics
Society and College of Radiographers
South Asian Health Foundation
South East Sheffield PCT
South West Kent PCT
Staffordshire Moorlands PCT
Stockport PCT
Sussex Cancer Network
Tameside and Glossop PCT
Taunton Road Medical Centre
Thames Valley Strategic Health Authority
Thames Valley Cancer Network
The Afiya Trust
UK Anaemia
UK National Screening Committee
UKHIFU
University College London Hospitals NHS Trust (UCLH)
University Hospital Aintree
University Hospital Birmingham NHSFT
University Hospitals Coventry & Warwickshire NHS Trust
University of Birmingham, Department of Primary Care & General Practice
University of North Durham
Velindre NHS Trust
Walsall PCT
<table>
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<th>Walsall Teaching PCT</th>
<th>Wiltshire PCT</th>
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<td>Wareney PCT</td>
<td>Wirral Hospital NHS Trust</td>
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<td>Welsh Assembly Government</td>
<td>World Cancer Research Fund International</td>
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<tr>
<td>Wessex Cancer Trust</td>
<td>Wyeth Pharmaceuticals</td>
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<td>West Cornwall PCT</td>
<td>Yamanouchi Pharma Ltd</td>
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<td>West Lincolnshire PCT</td>
<td>Yorkshire and the Humber Commissioning Group</td>
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<td>Whipps Cross University Hospital NHS Trust</td>
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Appendix 8.3

Individuals Carrying out 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  Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff
Victoria Titshall  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 Researcher
Dr Susanne Hempel  External Researcher
Dr Ailsa Snaith  External Researcher

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  Lecturer in Health Economics, London School of Health and Tropical Medicine
Dr Dyfrig Hughes  Director, Centre for the Economics and Policy in Health, University of Wales, Bangor

1 From Nov 2005 to December 2006.
2 From January 2007.
3 From Aug 2006.
4 From Nov 2005 to July 2006.
Prostate cancer: diagnosis and treatment

Dr Rhiannon Tudor Edwards4 Director, Centre for the Economics and Policy in Health, University of Wales, Bangor
Pat Linck4 Research Officer, Centre for the Economics and Policy in Health, University of Wales, Bangor
Eugenia Priedane4 Research Fellow, Centre for the Economics and Policy in Health, University of Wales, Bangor

Needs Assessment

Dr Sean McPhail3 Head of Cancer Analysis, Cancer Intelligence Service South West Public Health Observatory
Dr Tanya Cross4 South West Public Health Observatory

1 From Aug 2006.
2 From Nov 2005 to July 2006.
Appendix 8.4

Expert Advisers to the 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
Appendix 8.5

Members of the 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