Clinical Guideline

Prostate cancer: diagnosis and treatment

Full Guideline

Developed for NICE by the National Collaborating Centre for Cancer

Draft for consultation

FOREWORD

To be written by Dr Fergus Macbeth for the final version.

CONTENTS

Key Priorities

1. Men should be adequately informed about the effects of prostate cancer and the treatment options on their sexual function, appearance, continence and aspects of self-image. Healthcare professionals should support men and their partners to make treatment decisions taking into account the effects on quality of life as well as survival.

2. The man's decision whether or not to proceed to prostate biopsy should be informed by the prostate specific antigen (PSA) level, estimate of prostate size, digital rectal examination (DRE) findings, age, ethnicity, and comorbidities, together with any history of a previous negative prostate biopsy. The serum PSA level alone should not automatically lead to a prostate biopsy.

3. Men with localised low-risk prostate cancer should not routinely be offered immediate radical therapy. They should be offered watchful waiting or active surveillance, depending on their life expectancy and values.

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

5. Men and their partners should have early and ongoing access to specialist erectile dysfunction services.

6. Men with bothersome urinary symptoms should have access to specialist continence services for assessment, diagnosis and conservative treatment. This may include learning coping strategies, along with pelvic floor muscle re-education, bladder retraining and pharmacotherapy. Men with intractable stress incontinence should be referred to a specialist surgeon for consideration of an artificial urinary sphincter.

7. Biochemical relapse alone should not necessarily prompt an immediate change in treatment.

8. Hormonal therapy is not routinely recommended for men with biochemical relapse unless they have:
    a. symptomatic local disease progression; or
    b. any proven metastases; or
    c. a PSA doubling time <3months.

9. When men develop biochemical evidence of hormone refractory disease their management options should be discussed by the urology multidisciplinary team (MDT) with a view to seeking an oncological and/or specialist palliative care opinion as appropriate.

10. Palliative care should be available when needed and not limited to being available only at end of life. It should not be restricted to being associated with hospice care.

Key Research Recommendations

1. Research into the causes, and clinical trials of prevention and management of radiation-induced enteropathy should be undertaken.

   Radiotherapy remains the most common radical treatment for localised prostate cancer and is often associated with varying degrees of enteropathy. These effects may be early or late; short-lasting or long-lasting. The biological processes are poorly understood and the best way of preventing or managing the condition is unclear.

2. Further research should be conducted into the timing and effectiveness of treatments for erectile dysfunction after all treatments for prostate cancer.

   Erectile dysfunction is especially common after radical treatment for prostate cancer and also in more advanced disease. While effective treatments are available, it is not known which are most effective in this setting or when it is best to commence treatment.

3. More research should be conducted into the prevention and management of osteoporosis in men receiving long-term androgen withdrawal therapy.

   Androgen withdrawal therapy is sometimes used in men with advanced prostate cancer but it often causes loss of bone mineral and consequential bone fractures. The current evidence of commonly used interventions is insufficient to make conclusions about their clinical efficacy and cost effectiveness in this setting.

4. The role of radical surgery and extended lymphadenectomy as primary therapy for locally advanced prostate cancer should be studied in clinical trials.

   Lymph node involvement is a risk factor for death from prostate cancer. Some patients undergoing radical surgical treatment have involved margins (locally advanced disease) at resection. Others have extracapsular disease diagnosed prior to treatment decisions being made. It is not known if a radical attempt at cure with surgery improves survival.

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

   Many men with metastatic prostate cancer develop bone metastases. These are often painful and may result in serious spinal injury. In other cancer sites, e.g. breast, there is a demonstrable benefit from the use of bisphosphonates. However, there is insufficient evidence of a beneficial effect of their use in men with prostate cancer.

Recommendations

Chapter 2: Communication and Patient Centred Care

1. Recommendations on communication and patient centred care made in the two service guidance documents: "Improving Outcomes in Urological Cancers service guidance (NICE 2002)" and "Improving Supportive and Palliative Care for Adults with Cancer (NICE 2004)" should be followed throughout the patient journey.

2. Men with prostate cancer should receive individualised information tailored to their own needs. This information should be given by a clinician (consultant or specialist nurse) and may be supported by written and visual media.

3. Men should be offered advice about how to access information and support from the internet (including "*UK Prostate Cancer Link*") and other media, local and national cancer information services, and from cancer support groups.

4. When choosing or recommending information resources, healthcare professionals should ensure that their content is clear, reliable and up to date.

5. Healthcare professionals should seek and act on feedback from men with prostate cancer and their carers who use these resources.

6. Clinical staff caring for men with prostate cancer should ascertain the extent to which the man wishes to be involved in decision making and ensure that they have sufficient information to enable them to be so.

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

8. All relevant management options recommended in this guideline should be discussed whether or not they are available through local services.

9. Mechanisms should be put in place to ensure that, over prolonged periods of time, men and their primary care providers can gain access to specialist services.

10. Men should be adequately informed about the effects of prostate cancer and the treatment options on their sexual function, appearance, continence and aspects of self-image. Healthcare professionals should support men and their partners to make treatment decisions taking into account the effects on quality of life as well as survival.

11. Men and their partners should have the opportunity to discuss psychosexual issues with an appropriately skilled healthcare professional at any stage of the illness and its treatment.

Chapter 3: Diagnosis and Staging of Prostate Cancer

12. The man's decision whether or not to proceed to prostate biopsy should be informed by the prostate specific antigen (PSA) level, estimate of prostate size, digital rectal examination (DRE) findings, age, ethnicity, and comorbidities, together with any history of a previous negative prostate biopsy. The serum PSA level alone should not automatically lead to a prostate biopsy.

13. Men (and their partners) 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 significant increased chance of having to live with a prostate cancer diagnosis) and the potential benefits of prostate biopsy.

14. If the clinical suspicion of prostate cancer is high, because of a high PSA value and evidence of multiple bone metastases (positive isotope bone scan or sclerotic metastases on plain radiographs), prostate biopsy for histological confirmation should be omitted, unless this is required as part of a clinical trial.

15. Prostate biopsy should be carried out following the procedure recommended by the Prostate Cancer Risk Management Programme Document (PCRMP 2006).

16. The results of all prostate biopsies should be reviewed by a urological cancer multidisciplinary team (MDT). Men should only be re-biopsied after an MDT review of the risk characteristics including life expectancy, PSA, DRE, and prostate volume.

17. The provisional treatment intent (radical or not) should be determined before decisions on imaging are made.

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

19. Pelvic imaging is not recommended for men with low-risk disease (T1c or T2a, PSA≤10ng/ml, Gleason score ≤6).

20. Computerised Tomography (CT) imaging of the pelvis is not recommended for men with intermediate-risk disease (PSA 10-20ng/ml, or Gleason score 7, or clinical stage T2b or T2c)

21. Men with high-risk disease (T3, PSA>20ng/ml, or Gleason score 8-10) being considered for radical treatment should have pelvic imaging with either Magnetic Resonance Imaging (MRI), or CT if contraindicated.

22. Magnetic Resonance Spectroscopy (MRS) is not recommended except in the context of a clinical trial.

23. Isotope bone scintigraphy is not routinely recommended for men with low-risk disease.

24. Bone scanning should be performed when hormonal therapy is being deferred in high-risk, asymptomatic men.
25. Positron emission tomography (PET) imaging for prostate cancer is not recommended in routine clinical practice.

26. Nomograms should be used by doctors and patients in partnership to:
    a. aid decision making
    b. predict biopsy results
    c. predict pathological stage
    d. predict risk of treatment failure.

27. Where nomograms are used the reliability, validity and limitations of the prediction should be clearly explained, with appropriate support.

Chapter 4: Localised Prostate Cancer

28. Urological cancer MDTs should assign a risk category to all newly diagnosed men with localised prostate cancer.

29. Men who have chosen a watchful waiting regimen with no curative intent should normally be followed up in primary care. Investigations should not be performed unless symptoms occur and treatment is appropriate.

30. Men with localised low-risk prostate cancer should not routinely be offered immediate radical therapy. They should be offered watchful waiting or active surveillance, depending on their life expectancy and values.

31. Active surveillance is strongly recommended for men with a clinical stage T1c, a Gleason score 3+3, and with a PSA density <0.15ng/ml^2 and less than 50% of biopsy cores involved (<10mm of any 1 core involved).

32. Active surveillance can be recommended for other men with low-risk disease.

33. Active surveillance should be discussed as an option with men who have intermediate-risk disease.

34. Active surveillance is not recommended for men with high-risk localised disease.

35. For men on active surveillance the following regimen is recommended:
    - To reduce the sampling error associated with prostate biopsy, men who are candidates for active surveillance should have had at least 10 biopsy cores.
    - Repeat prostate biopsy should be performed at 1, 4 and 7 years, in accordance with the ProSTART trial protocol.
    - PSA should be tested every 3 months during the first 2 years and 6 monthly thereafter.
    - PSA velocity should be estimated by linear regression of PSA against time, using at least 5 PSA values over at least one year, and preferably over 2 or more years. A tool such as the Prostagram (http://www.mskcc.org/mskcc/html/10088.cfm) should be used.

- Indications for considering radical treatment include any of a PSA velocity >1ng/ml/year, higher-grade or more extensive disease on repeat biopsy, or evidence of locally advanced disease on DRE.
- The decision to proceed to radical treatment should be made in the light of the individual man's values, comorbidities and life expectancy.

36. Radical prostatectomy or radical radiotherapy (conformal or brachytherapy) should be considered for men with intermediate-risk localised prostate cancer.

37. Radical prostatectomy or radical radiotherapy (conformal) is recommended for men with high-risk localised prostate cancer.

38. For men receiving radical external beam radiotherapy for localised prostate cancer, 3D conformal radiotherapy should be used.

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

40. Given the range of treatment modalities and their serious side effects, men with prostate cancer who are candidates for radical therapies should have the opportunity to discuss their treatment options with both a specialist surgical oncologist and a specialist clinical oncologist.

41. Other radical therapies such as cryotherapy and high intensity focussed ultrasound (HIFU) are not recommended for men with localised or locally advanced prostate cancer other than in the context of controlled clinical trials.

42. Men presenting with symptoms consistent with radiation-induced enteropathy should be fully investigated, including flexible sigmoidoscopy, in order 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.

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

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

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

46. 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.

47. 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 if fertility is important to the man and/or his partner.

48. Men and their partners should have early and ongoing access to specialist erectile dysfunction services.

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

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

51. Men experiencing bothersome urinary symptoms before treatment should undergo urological assessment.

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

53. Men with bothersome urinary symptoms should have access to specialist continence services for assessment, diagnosis and conservative treatment. This may include learning coping strategies, along with pelvic floor muscle re-education, bladder retraining and pharmacotherapy. Men with intractable stress incontinence should be referred to a specialist surgeon for consideration of an artificial urinary sphincter.

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

55. The purpose, duration, frequency and location of follow-up should be discussed with each man, and where he wishes, his partner.

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

57. PSA levels should be checked at the earliest 6 weeks following treatment, at least 6 monthly for the first 2 years and then at least yearly thereafter.

58. Routine DRE is not recommended while the PSA remains at baseline levels.

59. After 2 years at the earliest, men with a stable PSA and no significant treatment complications, should be offered follow-up outside hospital, for example in primary care, by telephone or e-mail, or a combination, unless they are participating in a clinical trial which requires more formal clinic-based follow-up. The opportunity of direct access to the specialist team should be offered and explained.

60. Men who have chosen a watchful waiting regimen with no curative intent should normally be followed up in primary care.

Chapter 5: The Management of Relapse After Radical Treatment

61. Serial PSA levels after radical treatment should be analysed using the same assay technique.

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

63. Biopsy of the prostate after radiotherapy should only be done in men being considered for salvage local therapy in the context of clinical research.

64. Routine MRI scanning should not be performed prior to salvage radiotherapy.

65. An isotope bone scan should be performed if symptoms or PSA trends are suggestive of metastases.

66. Biochemical relapse alone should not necessarily prompt an immediate change in treatment.

67. Biochemical relapse should trigger an estimate of PSA doubling time, based on a minimum of 3 measurements over at least a 6 month period.

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

69. Men with biochemical relapse should be considered for entry to appropriate clinical trials, for example RADICALS.

70. Hormonal therapy is not routinely recommended for men with biochemical relapse unless they have:
    - symptomatic local disease progression; or
    - any proven metastases; or
    - a PSA doubling time <3months.

Chapter 6: Locally Advanced Prostate Cancer

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

72. Adjuvant hormonal therapy in addition to radical prostatectomy is not recommended, even in margin positive disease, other than in the context of a clinical trial, for example RADICALS.

73. Adjuvant hormonal therapy for up to 3 years is recommended for men receiving neoadjuvant hormonal therapy and radical radiotherapy for high-risk localised or locally advanced prostate cancer who have a Gleason score of ≥8.

74. Adjuvant hormonal therapy is not recommended for men with a Gleason score of ≤7.

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

76. Pelvic radiotherapy should be considered in men with >15% risk (estimated using the Roach formula (%LN risk = 2/3 PSA + [10x (Gleason score - 6)] of

pelvic lymph node involvement who are to receive neoadjuvant hormonal therapy and radical radiotherapy to the prostate.

77. Immediate post-operative radiotherapy after radical prostatectomy is not recommended, even in margin positive disease, other than in the context of a clinical trial, for example RADICALS.

Chapter 7: Metastatic Prostate Cancer

78. Bilateral orchidectomy should be recommended as an alternative to continuous LHRHa therapy.

79. Combined androgen blockade is not recommended as first-line treatment.

80. For men 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* is appropriate.

81. Men taking bicalutamide who do not maintain satisfactory sexual function, should stop bicalutamide and be treated with androgen withdrawal.

82. Intermittent androgen withdrawal may be offered as an alternative to continuous androgen withdrawal, especially to men with severe side effects.

83. Synthetic progestogens 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.

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

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

86. Men starting androgen withdrawal therapy should be informed that regular resistance exercise reduces fatigue and improves quality of life.

87. 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.

88. 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.

* BNF states that bicalutamide monotherapy should be at a dose of 150mg daily. A lower dose (50mg) is used for combined androgen blockade.

89. Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.

90. When men develop biochemical evidence of hormone refractory disease their management options should be discussed by the urology MDT with a view to seeking an oncological and/or specialist palliative care opinion as appropriate.

91. Dexamethasone at a dose of 0.5mg daily[†] is recommended as third line hormonal therapy after androgen withdrawal and anti-androgen therapy.

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

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

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

95. Bisphosphonates for pain relief may be considered when other treatments, including analgesics and palliative radiotherapy, have failed. The choice of drug should be based on the cost and either the oral or intravenous route of administration should be chosen according to convenience and tolerability.

96. Bisphosphonates should not be used routinely in men receiving androgen withdrawal therapy for prostate cancer.

97. The recommendations in the NICE Clinical Guideline on Osteoporosis should be followed once it is published.

98. Sr-89 should be considered for men with painful bone metastases from HRPC especially for men who are unlikely to receive myelosuppressive chemotherapy.

99. Upper urinary tract decompression 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.

100. The option of no intervention should also be discussed openly with men and remains a choice for some.

101. Men with metastatic prostate cancer should receive tailored information and access to specialist urology and palliative care teams to address their specific needs.

102. The regular assessment of needs (described in the NICE Guidance on 'Improving supportive and palliative care for adults with cancer') should be applied systematically to men with prostate cancer.

[†] Often used at higher doses in other indications

103. Men with metastatic prostate cancer should be given the opportunity to discuss their therapy and information needs with members of both urology and specialist palliative care teams when there are significant changes in their disease status or symptoms.

104. Palliative interventions at any stage should be integrated into co-ordinated care, and any transitions of care settings should be facilitated as smoothly as possible.

105. Men with prostate cancer, their partners and carers should be consulted as early as possible in respect of their values and preferences for palliative care. Treatment/care plans and preferred place of care should be tailored accordingly.

106. Palliative care should be available when needed and not limited to being available only at end of life. It should not be restricted to being associated with hospice care.

METHODOLOGY

1. Introduction

1.1 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 and Wales are produced as a response to a request from the Department of Health (DH) and the Welsh Assembly Government. They select 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.

1.2 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'.

The guideline is relevant to all healthcare professionals who come into contact with prostate cancer patients, as well as to the patients 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 patients.

1.3 The Remit of the Guideline

Guideline topics selected by the DH and the Welsh Assembly Government 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 treatments (covering surgical and chemical castration)***
- ***the role of tumour specific bisphosphonates.'***

1.4 What the Guideline Covers - The Scope

The remit was then translated into a scope document by the Guideline Development Group (GDG) Chair and Clinical Lead 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 from the DH/Welsh Assembly Government
- 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 (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 signed off by the GRP and posted on the NICE website.

1.5 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 at the start of the process and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered to the prostate cancer guideline can be found in Appendix 8.

1.6 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, to inform the development of the guideline. This document forms a supplement to the full guideline and will also appear on an accompanying CD-ROM when the guideline is published.

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.

2. The Process of Guideline Development – Who Develops the Guideline?

2.1 Overview

The development of this guideline was based upon methods outlined by the 'NICE guidelines manual' (NICE 2007). 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, define the scope which sets the parameters of the guideline
- forming the guideline development group
- developing clinical evidence-based 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.

2.2 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' (NICE 2007). The first step was to appoint a Chair and a Clinical Lead. Advertisements were placed for both posts and candidates were informally interviewed prior to being offered the role. The NCC-C Director, GDG Chair and Clinical Lead 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 Clinical Lead, 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).

2.3 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 day or two days) clinical questions and clinical and economic evidence were reviewed and 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 systematic reviewer, 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.

2.4 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.

2.5 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 (Appendix 8) who had been identified via the relevant registered stakeholder organisation. A full list of recognised experts who contributed to the guideline can be found Appendix 8. All relevant position papers are presented as part of the evidence review.

3. Developing Clinical Evidence-Based Questions

3.1 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 that 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 good 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

3.2 Method

An extensive list of potential topics for the guideline to investigate was complied by the NCC-C Director and GDG Chair and Clinical Lead 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 was 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.

3.3 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.

3.4 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 supplemental 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 Science1970 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 when the guideline is published).

3.5 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 reviewers assessed the quality of eligible studies by referring to the SIGN quality checklist for systematic reviews/meta-analyses and randomised control trials (Table 1). 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 (NICE 2007).

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

Table 1 Levels of evidence for intervention studies

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' (NICE 2007).

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.

3.6 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.

3.6.1 Economic Modeling

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 investigation. These 'economic priorities' were chosen on the basis of the following criteria, in broad accordance with the 'NICE guidelines manual (NICE 2007):

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 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 high 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.

3.7 Agreeing the Recommendations

For each clinical question the GDG were presented with a summary of the 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.

3.8 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, ten key priorities and 5 key research recommendations were selected by the GDG for implementation and patient algorithms agreed (see pages X-X for algorithms). To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

4. Consultation and Validation of the Guideline

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

Registered stakeholders (see Appendix 8) have 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.

5. 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).

6. 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 by the end of May 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 (NICE 2007). If not, the guideline will be updated approximately 4 years after publication.

7. Funding

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

8. 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

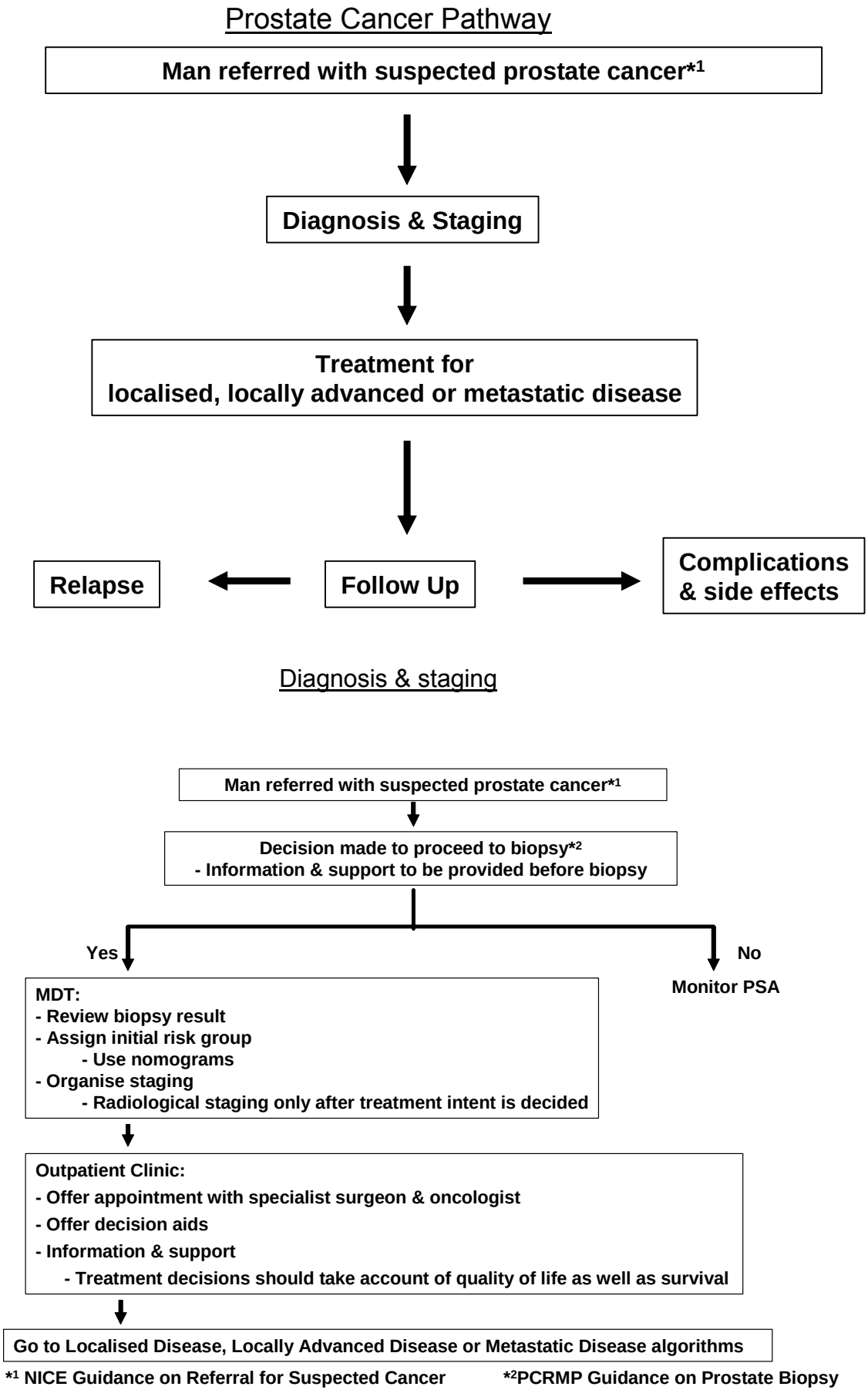
for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

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

References

National Institute for Health and Clinical Excellence (2007) The guidelines manual. London: National Institute for Health and Clinical Excellence.

Algorithm – a pictorial guide to show how the guideline is structured.



Localised Disease

	Low-risk *PSA <10ng/ml and Gleason score <=6 and T1c or T2a*	Intermediate-risk *PSA 10-20ng/ml or Gleason score 7 or T2b/c*	High-risk *PSA >20ng/ml* or Gleason score >= 8
Watchful Waiting	✓	?	?
Active Surveillance	✓	?	×
Brachytherapy	?	?	×
Radical Prostatectomy	?	?	✓
Radical Radiotherapy	?	?	✓
Cryotherapy	×	×	×
HIFU	×	×	×

- should be treatment of choice in low-risk
- repeat biopsy at 1, 4 & 7 years
- Measure PSA velocity

- 3D conformal radiotherapy
- Minimum dose 74Gy

✓	Preferred treatment
?	Treatment option – to be discussed with specialist urologist & oncologist
×	Not recommended

Locally Advanced Disease

T3a – T4 prostate cancer:

Radiotherapy & Hormonal Therapy:
- Neoadjuvant hormonal therapy
- Adjuvant hormonal therapy for Gleason >=8

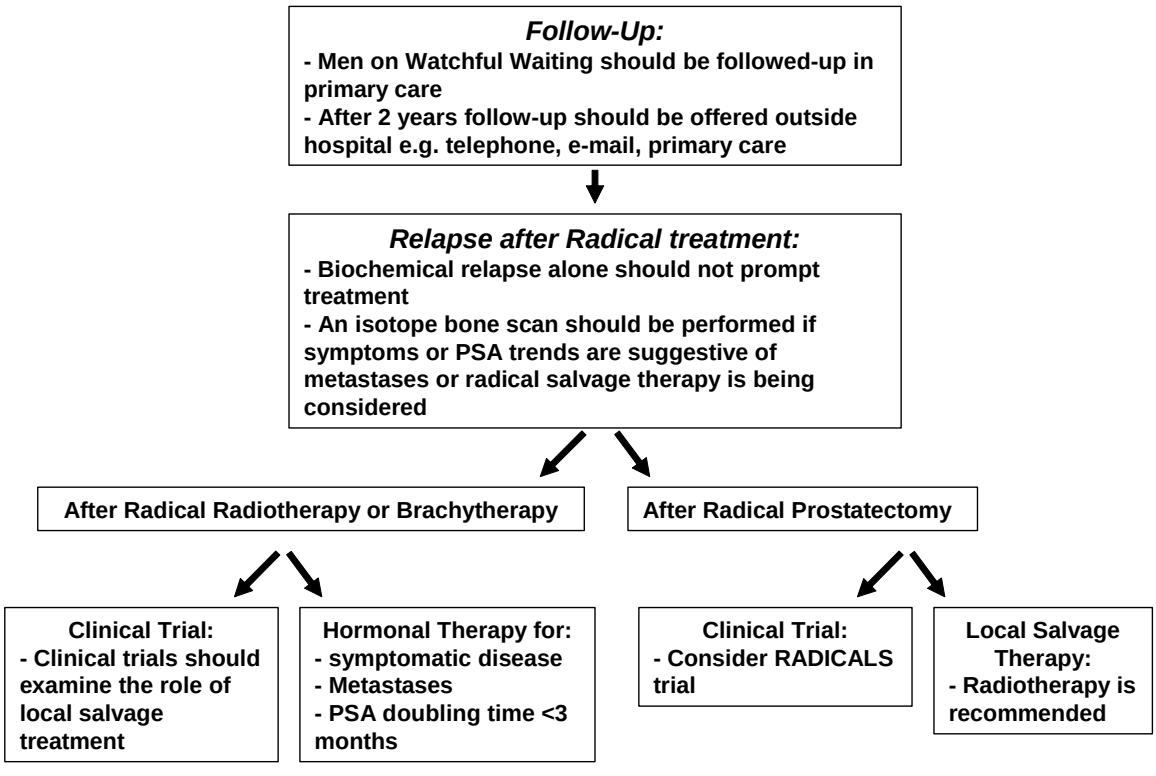
Hormonal Therapy alone:
- See Metastatic Disease

Bisphosphonates:
- ***Not recommended*** for prevention of bone metastases

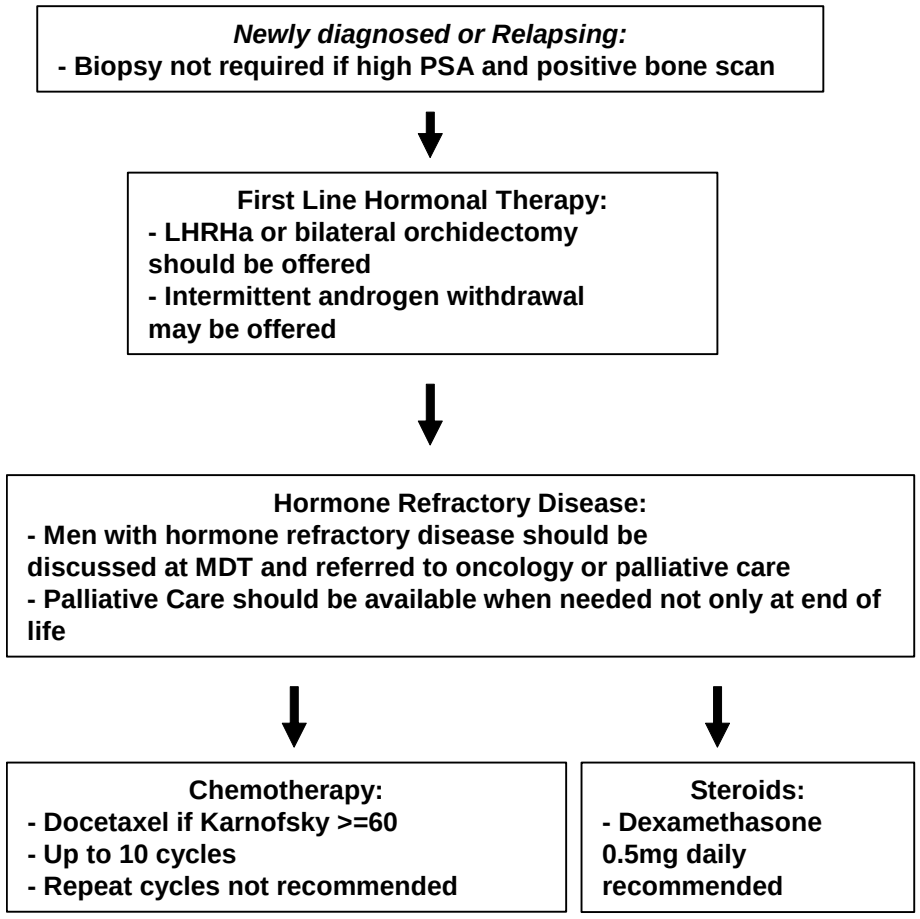
Post-Radical prostatectomy with extracapsular Spread:

Radiotherapy:
- Immediate post-op radiotherapy ***not recommended***
- Adjuvant hormonal therapy ***not recommended***

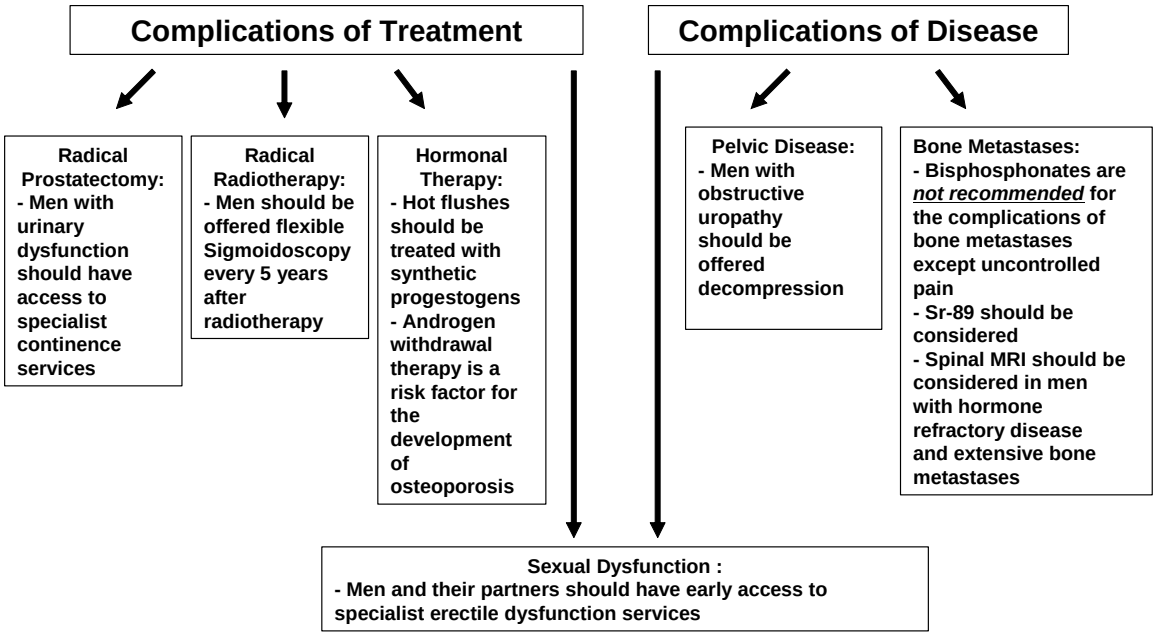
Follow-Up & Relapse after Radical Treatment



Metastatic Disease



Management of Complications & Side Effects of Treatment



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 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).

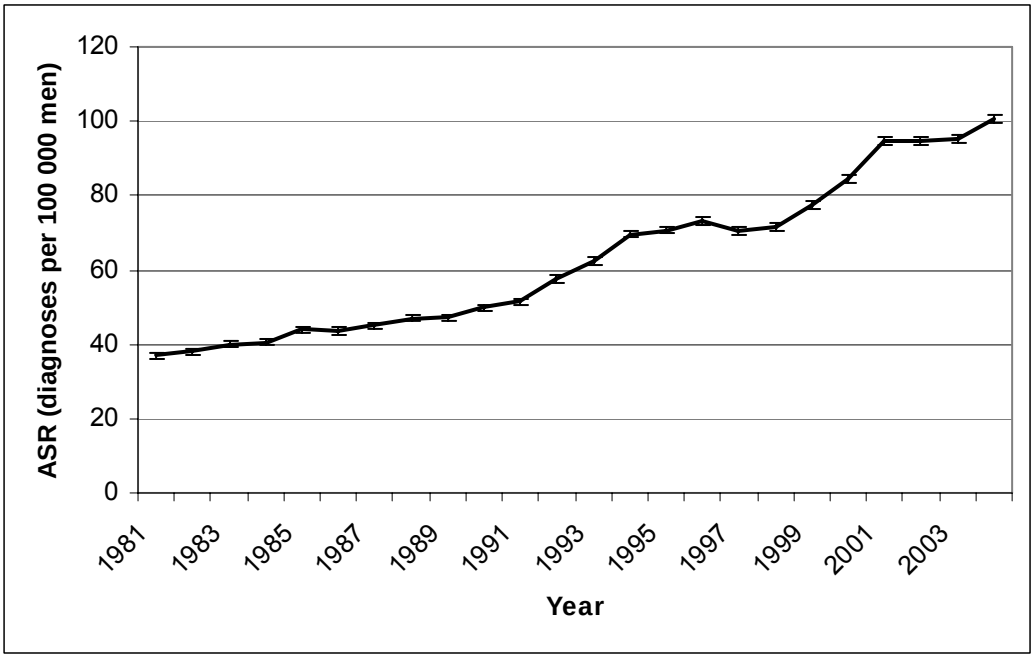


Figure 1.1, Directly Age Standardised Rate (ASR) of prostate cancer incidence in England and Wales (to European standard population). Data source: Office of National Statistics MB1 series and Welsh Cancer Intelligence unit and Surveillance (WCISU).

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.

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.

[‡] Data Source: cancer registries of England and Wales

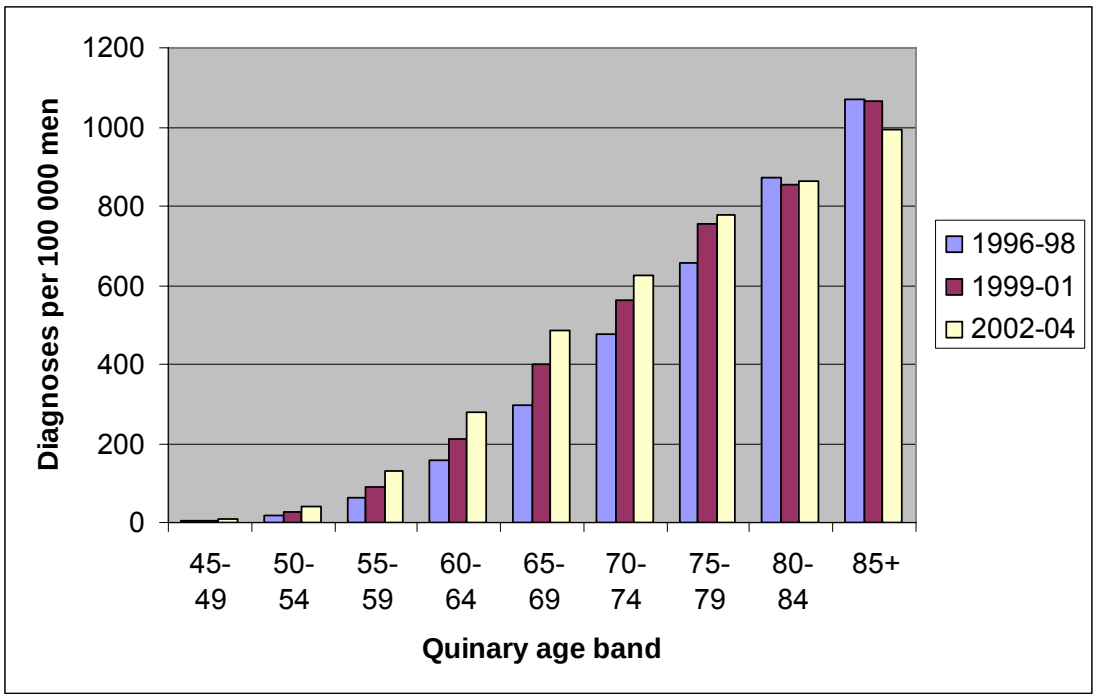


Figure 1.2 rate of diagnosis of prostate cancer by 5-year age band. Data source: cancer registries of England and Wales.

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)

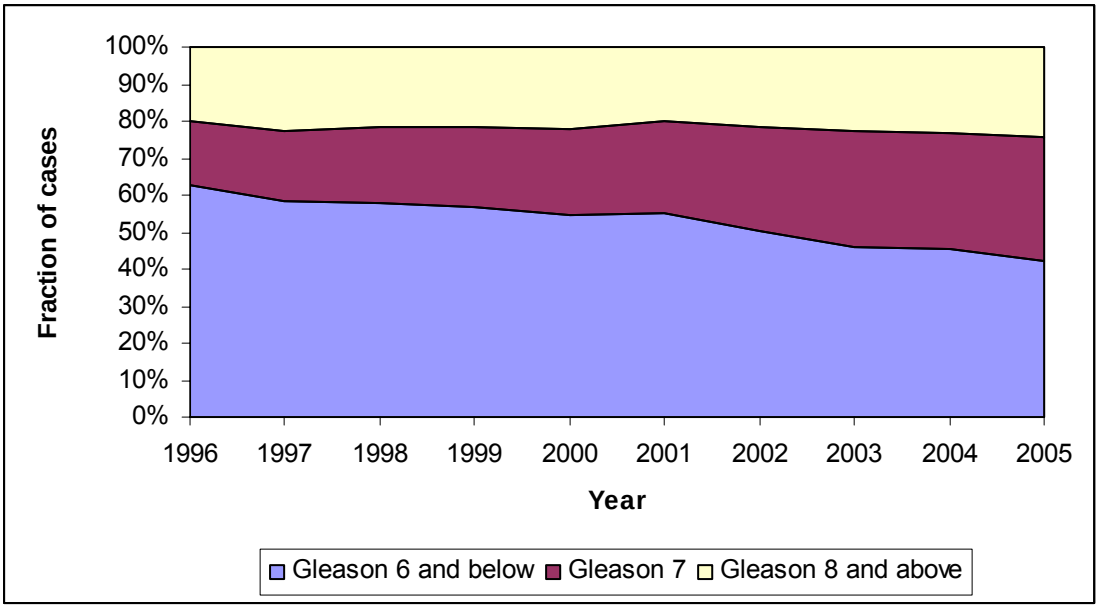


Figure 1.3, Stacked plot of prostate cancer diagnoses broken down by Gleason score (where the score is recorded) for the South West of England. Data source: British Association of Urological Surgeons registry database and South West Public Health Observatory

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 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 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.

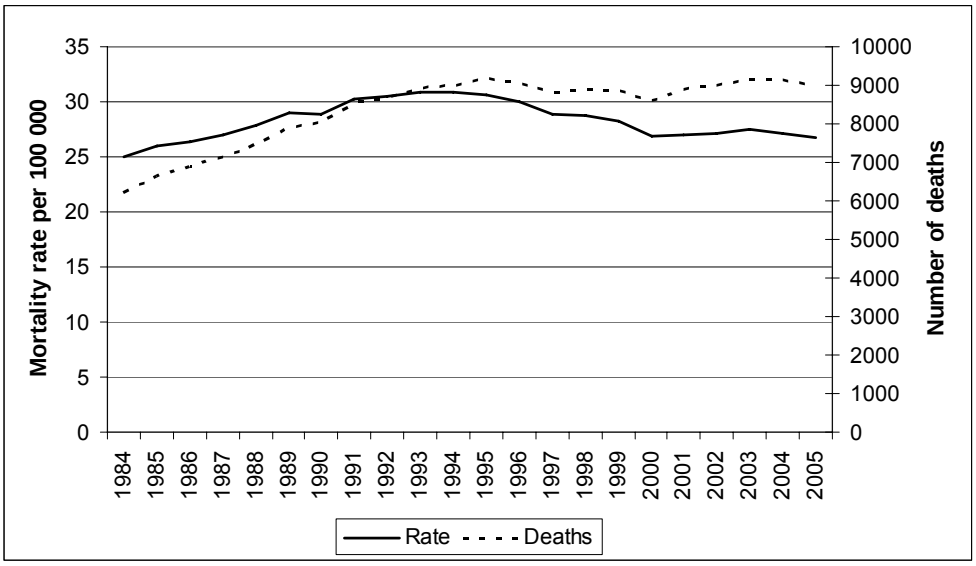


Figure 1.4, Directly Age Standardised mortality Rate (to European Standard population) and number of deaths from prostate cancer in England and Wales 1984-2005. Data source: Office of National Statistics.

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 Source: cancer registries of England and Wales
[**] Data Source: Office of National Statistics and Ordnance Survey

Data from the American Surveillance, Epidemiology and End Results (SEER) database (www.seer.cancer.gov/) and the UK PROCESS study (Ben-Schlomo Y, 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.

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 prostate-specific antigen (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.

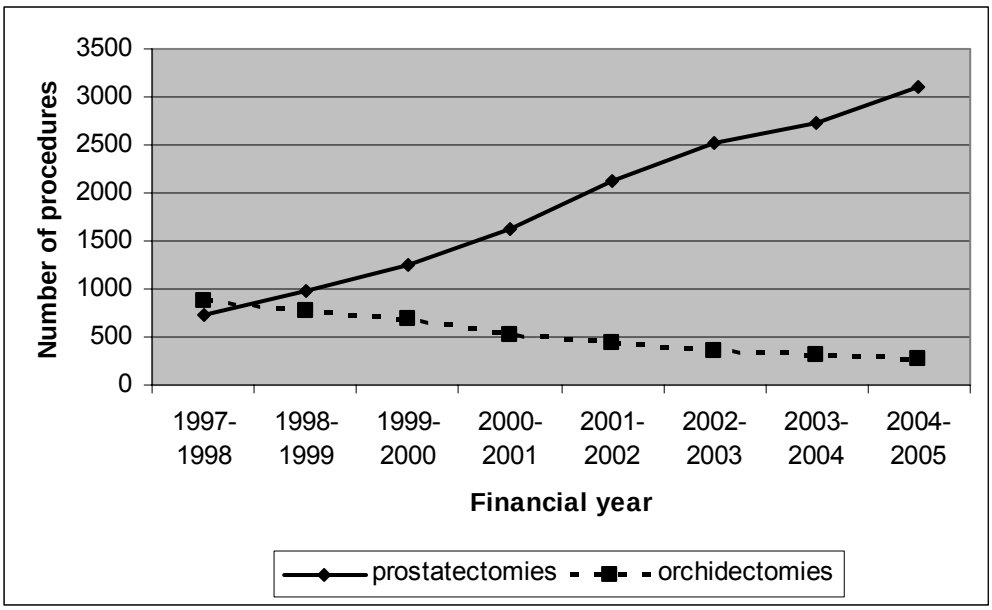


Figure 1.5, Numbers of all radical prostatectomy and orchidectomy operations on prostate cancer patients in England. Prostatectomies defined by OPCS code M61, Orchidectomies are defined by OPCS codes N05 and N06. Data source: HES data provided by NATCanSAT.

Metastatic prostate cancer can be treated by the surgical removal of the testes, otherwise known as orchidectomy (Cancer Research UK [online]). 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)[††]. 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 remarkable consistent, between 371 and 387.

[††] Data source: BAUS cancer registry

1.7 Hormonal Therapy

Hormonal therapy prescriptions have increased dramatically since the mid-1980s[‡‡]. Anti-androgen prescriptions rose from zero prior to 1983 to approximately 150,000 per annum in 2004. Prescriptions for luteinising hormone-releasing hormone agonists (LHRHa) 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[§§]. Clear differences in the patterns of dose and fractionation occur across NHS trusts, indicating a variation in practice[***].

1.9 The Findings of Cancer Peer Review of Urology Cancer Teams in England 2004-2007

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 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%).

[‡‡] Data Source: IMS Health Medical Data Index, London
[§§] Data Source: South West Public Health Observatory and RES dataset provided by NatCanSAT
[***] Data Source: RES data provided by NATCanSAT

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 in 2003-4, which can be attributed mainly to the creation of the NCRI and the NCRN.

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2. COMMUNICATION AND PATIENT CENTRED CARE

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 (WAG 2005) and The Department of Health (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 (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 informed 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.

Recommendation

- Recommendations on communication and patient centred care made in the two service guidance documents: 'Improving Outcomes in Urological Cancers' (NICE 2002) and 'Improving Supportive and Palliative Care for Adults with Cancer' (NICE 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.

Recommendations

- Men with prostate cancer should receive individualised information tailored to their own needs. This information should be given by a clinician (consultant or specialist nurse) and may be supported by written and visual media.
- Men should be offered advice about how to access information and support from the internet (including "UK Prostate Cancer Link" http://www.prostate-link.org.uk/) and other media, local and national cancer information services, and from cancer support groups.
- When choosing or recommending information resources, healthcare professionals should ensure that their content is clear reliable and up to date.
- Healthcare professionals should seek and act on feedback from men with prostate cancer and their carers who use these resources.
- Clinical staff caring for men with prostate cancer should ascertain the extent to which the man wishes to be involved in decision making and ensure that they have sufficient information to enable them to do so.

Qualifying Statement: There was GDG consensus in support of these recommendations, based on evidence of unmet need.

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 Guideline Development Group 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
- guiding the patient through each step in making a decision, taking into account his or her own beliefs and values.

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

Recommendation

- A validated, up-to-date decision aid is recommended for use in all urology cancer teams. It should be offered to men with localised prostate cancer when making treatment decisions, by healthcare professionals trained in its use[†††].

Qualifying statement: This recommendation was based on a combination of high quality evidence and GDG consensus.

Clinical Evidence

Evidence about the effectiveness of decision aids comes from a systematic review of randomised trials in a range of conditions, including 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 Guideline Development Group did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Recommendation

- All relevant management options recommended in this guideline should be discussed whether or not they are available through local services.

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

[†††] a decision aid specific for men with localised prostate cancer is in development and publication is expected in 2008.

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

- Mechanisms should be put in place to ensure that, over prolonged periods of time, men and their primary care providers can gain access to specialist services.

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

2.4.1 Prostate Cancer and the Effect it May Have on Men's Sense of Masculinity

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

- Men should be adequately informed about the effects of prostate cancer and the treatment options on their sexual function, appearance, continence and aspects of self-image. Healthcare professionals should support men and their partners to make treatment decisions taking into account the effects on quality of life as well as survival.
- Men and their partners should have the opportunity to discuss psychosexual issues with an appropriately skilled healthcare professional at any stage of the illness and its treatment.

Qualifying statement: This recommendation is 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 Guideline Development Group 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.

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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 2005) .

It has been normal practice that men who are found to have an abnormal serum prostate specific antigen (PSA) [*] level should have a prostate biopsy. For example, the UK Prostate Cancer Risk Management Program 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 (ref), 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) (ref) 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, do 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 digital rectal examination (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 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.

[*] For more information on PSA please see Appendix 1

Recommendations

- The man's decision whether or not to proceed to prostate biopsy should be informed by the PSA level, estimate of prostate size, digital rectal examination (DRE) findings, age, ethnicity, and comorbidities, together with 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) 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 significant increased chance of having to live with a prostate cancer diagnosis) and the potential 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, lower urinary tract symptoms and prostate volume.

Health Economic Evaluation

The Guideline Development Group 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 multiple bone metastases (positive isotope bone scan or sclerotic metastases on plain radiographs), prostate biopsy for histological confirmation should be omitted, 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 (Vandecandelaere *et al.* 2004; Katagiri *et al.* 1999) suggested the prevalence of prostate cancer in men presenting with bone metastases and unknown primary tumour was around 30%. Case series (Wymenga *et al.* 2001; Gleave *et al.* 1996; O'Sullivan *et al.* 2003; Lin *et al.* 1999; Oesterling 1993) provide evidence about PSA

concentration and bone scan results in men with histologically confirmed (but untreated) prostate cancer. These studies allow estimates of the sensitivity of various PSA cut-offs for the detection of prostate cancer in men with bone metastases. A systematic review (Eichler *et al.* 2006) identified 36 studies with data about adverse effects associated with prostate biopsy. The most common were minor bleeding, voiding difficulties and minor infection.

Health Economic Evaluation

The Guideline Development Group 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 trans-urethral resection of the prostate (TURP) or holmium laser resection of the prostate (HoLeP).

The Prostate Cancer Risk Management Programme (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

- Prostate biopsy should be carried out following the procedure recommended by the Prostate Cancer Risk Management Programme document (PCRMP 2006)
- The results of all prostate biopsies should be reviewed by a urological cancer multidisciplinary team (MDT). Men should only be re-biopsied after an MDT review of the risk characteristics including life expectancy, PSA, DRE, and prostate volume.

Qualifying statement: These recommendations, are 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. Five 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) 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 Guideline Development Group 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 *pathologic stage* is based on the surgical removal and histological examination of the entire prostate gland, the seminal vesicles and surrounding structures and, if relevant, pelvic lymph nodes.

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

3.3.1 Imaging at the Time of Diagnosis for Prostate Cancer

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

Recommendations

- The provisional treatment intent (radical or not) should be determined 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 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 <10ng/ml, Gleason score ≤6, and clinical stage T1c or T2a
- Intermediate-risk - PSA 10-20ng/ml, or Gleason score 7, or clinical stage T2b or T2c
- High-risk - PSA >20ng/ml, or Gleason score 8-10, or clinical stage T3.

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

3.3.2 Imaging for T-Staging and N-Staging

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

Recommendation

- Pelvic imaging is not recommended for men with low-risk disease (T1c or T2a, PSA≤10ng/ml, Gleason score ≤6).

Qualifying statement: There was GDG consensus that imaging would not affect the treatment decision.

Recommendation

- CT imaging of the pelvis is not recommended for men with intermediate-risk disease (PSA 10-20ng/ml, or Gleason score 7, or clinical stage T2b or T2c).

Qualifying statement: there is not enough evidence to support the routine use of CT in men with intermediate-risk disease.

Recommendation

- Men with high-risk disease (T3, PSA>20ng/ml, or Gleason score 8-10) being considered for radical treatment should have pelvic imaging with either MRI, or CT if contraindicated.

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

Recommendation

- MRS is not recommended 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.

Two studies (reviewed in National Institute for Clinical Excellence 2002) showed better staging accuracy with MRI than with CT. Other systematic reviews have considered the staging accuracy of MRI (Engelbrecht *et al.* 2002b; 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 1 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 therapy was intended compared with no MRI, in people 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.

3.3.3 Imaging for M-Staging

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

Recommendation

- Isotope bone scintigraphy is not routinely recommended for men with low-risk disease.

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

Two systematic reviews (Abuzallouf *et al.* 2004 National Institute for Clinical Excellence 2002) looked at the role of radioisotope bone scans in the staging of men with newly diagnosed prostate cancer. Abuzallouf and co-workers (Abuzallouf *et al.* 2004) 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 (National Institute for Clinical Excellence 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 10ng/ml were unlikely to have a positive bone scan.

Health Economic Evaluation

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

Recommendation

- Bone scanning should be performed when hormonal therapy is being deferred in high-risk, asymptomatic men.

Qualifying Statement: In the absence of any evidence there was GDG consensus that making this recommendation would reduce the risk of patients developing spinal cord compression.

Clinical Evidence

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 therapy is not intended. Small case series (Noguchi *et al.* 2003; Yamashita *et al.* 1993; Knudson *et al.* 1991) reported outcomes in men with positive bone scans at presentation. Two of these series (Noguchi *et al.* 2003; Knudson *et al.* 1991) found extensive disease on bone scan was an adverse prognostic factor for survival. There is observational evidence (Bayley, 2004; Venkitaraman, 2007) that extensive disease on bone scan is an independent risk factor for spinal cord compression in men without functional neurological impairment.

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.

3.3.4 Role of PET in Staging Prostate Cancer

Positron-Emission Tomography (PET) imaging using the radiopharmaceutical agent 18-FDG does not reliably show primary prostate cancer. This is because of the relatively low metabolic activity in tumours which are slow-growing and because the radiopharmaceutical agent accumulates in the bladder, obscuring the prostate. Newer positron-emitting tracers are under evaluation. These include 11-C acetate which has a high specificity for prostate cancer, 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. Nomograms have been developed from outcome data on large groups of men with prostate cancer. Using predictive factors such as T-stage, Gleason score, PSA and histology results they can be used to estimate the risk of metastatic spread, lymph node involvement or recurrence following treatment. There is a wide variation in incidence rates between North America and the UK so that a nomogram developed in a screened population in the USA may not be wholly relevant to an unscreened population in this country and therefore need to be used with caution. Most nomograms in current use have been developed on patient groups outside the UK.

Recommendation

- Nomograms should be used by doctors and patients in partnership to:

  a. aid decision making
  b. predict biopsy results
  c. predict pathological stage
  d. predict risk of treatment failure.

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

Recommendation

- Where nomograms are used the reliability, validity and limitations of the prediction should be clearly explained, with appropriate support.

Qualifying statement: In the absence of evidence on 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 outside the UK, that nomograms can accurately identify risks for men with prostate cancer. Most nomograms have been developed for use in men with clinically localised disease who are candidates for radical prostatectomy, and these are also the most widely validated. Although only one UK validation study was found, some nomograms have been validated in other western European countries.

Health Economic Evaluation

The Guideline Development Group 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 (T2b or T2c, or PSA 10-20ng/ml, or Gleason score 7) to inform management decisions.
- More research is recommended into the use of MRS in prostate cancer.

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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, Gleason score ≤6, and clinical stage T1c or 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 (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.

[‡‡‡] 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 Guideline Development Group 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).

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
- High intensity focussed ultrasound (HIFU)
- Cryotherapy.

Watchful Waiting

Traditional watchful waiting involves the conscious decision to avoid treatment unless symptoms of progressive disease develop. Those men who do develop symptoms of progressive disease are usually managed with hormonal therapy. This approach is

most often offered to older men, or those with significant co-morbidities who are thought unlikely to have significant cancer progression during their likely natural life span.

Recommendation

- Men who have chosen a watchful waiting regimen with no curative intent should normally be followed up in primary care. Investigations should not be performed unless symptoms occur and treatment is appropriate.

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

Active Surveillance

The aim 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. Men on active surveillance are monitored by serial PSA estimations, and repeat prostate biopsy. Those who have evidence of disease progression, in terms of the rate of rise of PSA or adverse findings on repeat biopsy, are offered curative treatment. Active surveillance is therefore an option for men with low-risk disease who are fit for radical treatment in the event of 'disease progression'.

Recommendation

- Men with localised low-risk prostate cancer should not routinely be offered immediate radical therapy. They should be offered watchful waiting or active surveillance, depending on their life expectancy and values.

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

Recommendations

- Active surveillance is strongly recommended for men with a clinical stage T1c, a Gleason score 3+3, and with a PSA density <0.15ng/ml^2 and less than 50% of biopsy cores involved (<10mm of any 1 core involved).
- Active surveillance can be recommended for other men with low-risk disease.
- Active surveillance should be discussed as an option with men who have intermediate-risk disease.
- Active surveillance is not recommended for men with high-risk localised disease.

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.

Recommendations

For men on active surveillance the following regimen is recommended:

- To reduce the sampling error associated with prostate biopsy, men who are candidates for active surveillance should have had at least 10 biopsy cores.
- Repeat prostate biopsy should be performed at 1, 4 and 7 years, in accordance with the ProSTART trial protocol (Klotz online).
- PSA should be tested every 3 months during the first 2 years and 6 monthly thereafter.
- PSA velocity should be estimated by linear regression of PSA against time, using at least 5 PSA values over at least one year, and preferably over 2 or more years. A tool such as the Prostagram (http://www.mskcc.org/mskcc/html/10088.cfm) should be used.
- Indications for considering radical treatment include any of a PSA velocity >1 ng/ml/year, higher-grade or more extensive disease on repeat biopsy, or evidence of locally advanced disease on digital rectal examination (DRE).
- The decision to proceed to radical treatment should be made in the light of the individual man's values, 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.

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 transrectal ultrasound (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.

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. It is possible that improved continence and potency rates will also be seen. Radical prostatectomy is a major operation, and is typically only offered to men under 70 years of age.

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 implanted 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.

There is no good quality research comparing any of the above 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. High intensity focused ultrasound (HIFU) and cryotherapy have become further options requiring evaluation.

HIFU and Cryotherapy

HIFU is a therapy which aims to eradicate prostate cancer by heating the gland using ultrasound. Cryotherapy is another treatment which aims to eradicate prostate cancer by freezing the gland.

Long term data on disease control are available for radical prostatectomy, external beam radiotherapy and brachytherapy. There is little good quality information available on disease control and toxicity of HIFU and cryotherapy.

Recommendations

- Radical prostatectomy or radical radiotherapy (conformal or brachytherapy) should be considered for men with intermediate-risk localised prostate cancer.
- Radical prostatectomy or radical radiotherapy (conformal) is 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.

Recommendation

- For men receiving radical external beam radiotherapy for localised prostate cancer, 3D conformal radiotherapy should be used.

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

Recommendation

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

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

Recommendation

- Given the range of treatment modalities and their serious side effects, men with prostate cancer who are candidates for radical therapies 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.

Recommendation

- Other radical therapies such as cryotherapy and HIFU are not recommended for men with localised or locally advanced prostate cancer other than in the context of controlled clinical trials.

Qualifying statement: There is insufficient evidence of the balance between clinical benefit and harm for these treatments.

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.

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 two systematic reviews of case series (Hummel *et al.* 2003; National Institute for Health and Clinical Excellence 2005). Both 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.

HIFU

All the included studies were case series (Beerlage *et al.* 1999; Chaussy & Thuroff 2003; Gelet *et al.* 1999; Gelet *et al.* 2000; Poissonnier *et al.* 2003; Thuroff *et al.* 2003; Uchida *et al.* 2002; Uchida *et al.* 2005). Follow-up in these series was short and only one of the studies had a median follow-up of more 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 and Konski et al. 2006).

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

[§§§] 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.

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.

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 quality-adjusted life-years (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 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 1: Baseline incremental cost-effectiveness ratios

	Cost	LY	QALYs[1]	QALYs[2]
WW	£6185	9.69	6.96	6.63
RP	£10619	10.19	7.52	6.36
ICER		£8868	£7918	**Dominated**

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

In QALYs[1], there is 0 probability of complications following treatment whereas in QALYs[2], the additional probabilities of urinary obstruction, urinary leakage and impotence are assumed.
The figure in bold represents the main baseline result. In this instance, RP is more costly and less effective than WW, thus it is 'dominated'.

Threshold analysis was conducted in order to see how effective, in terms of extra QALYs, other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to be in order for them to be cost-effective (compared to watchful waiting). The analysis showed that the remaining treatment options would need to produce between 0.08 and 0.36 additional QALYs compared to watchful waiting in order for them to be considered cost-effective at the £30,000 per additional QALY level (Table 2).

Table 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.

Treatment	Expected Cost of Treatment	Required QALY Increase[a]	Equivalent Health Gain In Months[b]
External beam radiotherapy	£8618	0.08	1
Brachytherapy	£11320	0.17	2
Cryotherapy	£12958	0.23	2.8
IMRT	£15016	0.29	3.5
HIFU	£17816	0.36	4.3

IMRT – intensity modulated radiotherapy; HIFU – high intensity focussed 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 0.08 QALYs.

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 up date of this model, as both are collecting adverse event data associated with treatment options for men with localised prostate cancer, including radical prostatectomy.

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

4.5 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.

4.5.1 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.

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 flexible sigmoidoscopy, in order 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 follow-up with 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 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 Guideline Development Group did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

4.5.2 Sexual Dysfunction

Sexual dysfunction is a very common side effect of all treatments for localised prostate cancer. Sexual dysfunction is a general term which includes loss of libido, erectile dysfunction, infertility and psychosexual issues.

The risk of loss of sexual function has an important influence on the decisions which men and their partners make about treatment for prostate cancer. Although there is evidence that, following an initial loss of erectile function, spontaneous improvements will occur in a proportion of men without specific intervention, most men who undergo radical treatment for prostate cancer experience erectile dysfunction and this is a cause of distress for the majority (see Chapter 2).

Recommendation

- Prior to 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.

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 if fertility is important to the man and/or his partner.

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

Recommendation

- Men and their partners should have early and ongoing access to specialist erectile dysfunction services.

Qualifying statement: There was GDG consensus to support making this recommendation.

Recommendation

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

Qualifying statement: Evidence from randomised trials has shown a clinical benefit for intervention with PDE5 inhibitors.

Recommendation

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

Qualifying statement: This recommendation is based on evidence from observational studies.

Clinical Evidence

There is good evidence, from placebo controlled randomised trials, that sildenafil improves erectile function in men with erectile dysfunction after radical prostatectomy (Carson et al. 2002) and external beam radiotherapy (Incrocci et al. 2001). In placebo controlled trials, tadalafil (Montorsi et al. 2004) and vardenafil (Brock et al. 2003) improved erectile function in patients with 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 therapy 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 Guideline Development Group did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

4.5.3 Urinary Incontinence

Urinary incontinence of all types has been reported after prostate cancer treatment. Radical prostatectomy can especially lead to stress incontinence, which may be temporary or permanent. Incontinence may be a problem after brachytherapy and external beam radiotherapy, in those men who have also had a trans-urethral resection of the prostate. The severity of the symptoms is very variable as is the degree to which this bothers individual men. Treatments for incontinence include physical (pelvic floor muscle training, bladder retraining), medical (drug therapy) or surgical (injection of bulking agents, artificial urinary sphincters or perineal sling). Slings are currently under evaluation.

Recommendations

- Men experiencing bothersome urinary symptoms before treatment should undergo urological assessment.
- Men undergoing treatment for prostate cancer should be warned of the likely effects of the treatment on their urinary function.

Qualifying statement: There was case series evidence supported by GDG consensus that these recommendations should be made.

Recommendation

- Men with bothersome urinary symptoms should have access to specialist continence services for assessment, diagnosis and conservative treatment. This may include learning coping strategies, along with pelvic floor muscle re-education, bladder retraining and pharmacotherapy. Men with intractable stress incontinence should be referred to a specialist surgeon for consideration of an artificial urinary sphincter.

Qualifying statement: There was strong GDG consensus and evidence from randomised trials to support making this recommendation.

Recommendation

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

Qualifying statement: The evidence from one small randomised trial did not support the use of this intervention.

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 1 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 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 out patient visits to hospital doctors. Alternative models include telephone follow-up, nurse-led clinics, and follow-up in primary care. Although follow-up needs to be long term, this does not necessarily need to be hospital-based.

Recommendations

- The purpose, duration, frequency and location of follow-up should be discussed with each man, and where he wishes, his partner.
- Men should be clearly advised about potential longer term adverse effects and when and how to report them.
- PSA levels should be checked at the earliest 6 weeks following treatment, at least 6 monthly for the first 2 years and then at least yearly thereafter.
- Routine DRE is not recommended while the PSA remains at baseline levels.
- After 2 years at the earliest, men with a stable PSA and no significant treatment complications, should be offered follow-up outside hospital, for example in primary care, by telephone or e-mail, or a combination, unless they are participating in a clinical trial which requires more formal clinic-based follow-up. The opportunity of direct access to the specialist team should be offered and explained.
- Men who have chosen a watchful waiting regimen with no curative intent should normally be followed up in primary care.

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

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.*).

Health Economic Evaluation

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

Research Recommendations

- 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.

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5 THE MANAGEMENT OF 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 therapy 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 therapy. Radical surgery aims to remove all prostatic tissue. The serum PSA should drop to very low levels (typically <0.01ng/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 therapy 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

- Serial PSA levels after radical treatment should be analysed using the same assay technique.

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

5.2.1 After Radical Prostatectomy

The presence of any detectable PSA in peripheral blood is often interpreted as indicating a clinically significant relapse, but this may be due to the presence of benign prostate tissue in a small proportion of men. The existence of residual disease, which may lead to clinical progression, can be recognised most reliably by a PSA of >0.4ng/ml and rising.

5.2.2 After Radical Radiotherapy

The PSA does not usually fall to zero after radical treatment with external beam

[****] For more information on PSA please see Appendix 1

radiotherapy. The definitions of biochemical relapse with the best combination of sensitivity and specificity for clinical or distant relapse after radical therapy 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 + 2ng/ml: Roach, 2006), had a sensitivity of 74% and specificity of 71% for any clinical failure.

5.2.3 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 + 2ng/ml.

Clinical Evidence

Evidence from case series and clinical trials shows that 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 3ng/ml) above the current nadir value at call. The 2005 ASTRO consensus definition (PSA greater than current nadir + 2ng/ml at call: Roach, 2006), had a sensitivity of 74% and specificity of 71% for any clinical failure.

After brachytherapy
Kuban et al. (2006) reported the most sensitive and specific practical definitions of biochemical recurrence after brachytherapy were the current nadir + 1ng/ml and the current nadir + 2ng/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 Guideline Development Group 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 by a rising PSA as defined above, options for investigation may include biopsy, local (pelvic) imaging and imaging for the presence of metastatic disease.

5.3.1 Biopsy

Biopsy of the prostatic bed after radical prostatectomy can identify the existence of local recurrence. However, a positive biopsy does not exclude metastatic disease and a negative biopsy does not exclude local recurrence. Therefore the results of the biopsy are not useful for making treatment decisions. After radiotherapy, including brachytherapy, routine biopsy of the prostate does not add clinically useful information to that obtained from serial PSA measurement.

Recommendations

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

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

Clinical Evidence

The literature search found no studies reporting the impact of staging after biochemical recurrence on patient outcomes. 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 Guideline Development Group did not rate this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

5.3.2 Imaging

Magnetic Resonance Imaging (MRI) scanning may have some value in those with biochemical relapse being considered for further local therapy. It may detect significant extracapsular disease, seminal vesicle involvement or lymphadenopathy which might preclude radical salvage therapy.

The chance of finding skeletal metastases in men with biochemical relapse is best predicted by the absolute PSA level and the rate of rise.

Recommendations

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.
- An isotope bone scan should be performed 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 10ng/ml (Okotie et al. 2004).

In one series salvage treatment decisions were sometimes changed on the basis of ProstaScint imaging (Jani 2004), however there was inconsistent evidence that ProstaScint results could predict the outcome of salvage therapy (Levesque et al. 1998; Proano 2006; Mohideen 2002; Thomas et al. 2003).

Health Economic Evaluation

The Guideline Development Group 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 therapy, 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 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.

5.4.1 Local Salvage Therapy

5.4.1.1 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.

Recommendation

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

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

Recommendation

- Men with biochemical relapse should be considered for entry to appropriate clinical trials, for example RADICALS.

Qualifying statement: These recommendations are based on GDG consensus.

5.4.1.2 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.

5.4.2 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 biochemical relapse unless they have:
  - symptomatic local disease progression; or
  - any proven metastases; or
  - a PSA doubling time <3months.

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) and complication rates (Stephenson et al. 2004; Ward et al. 2005) are derived from case series. The NICE interventional procedures guidance on salvage cryotherapy (National Institute for Health and Clinical Excellence 2005) reviewed seven case series with limited follow-up. Five year disease specific survival was 79%, in the only study reporting this outcome**.**

A systematic review (Nilsson, Norlen, & Widmark 2004) of ten retrospective case series, concluded that after radical prostatectomy (with adverse factors) adjuvant EBRT seems to result in better disease free survival than salvage or no postoperative EBRT. Similarly salvage EBRT probably results in marginally better outcome than no salvage EBRT. One study (Macdonald *et al.* 2004) reported outcomes after salvage radiotherapy in a series of men with biochemical recurrence only and in men with palpable recurrence. Five year overall survival was 95% in men treated for biochemical recurrence compared to 76% for men with palpable recurrence.

The literature search did not identify any randomised trials of the treatment of PSA-only recurrence. Indirect evidence comes from a systematic review (Wilt *et al.* 2001) of four randomised control trails (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.

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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.

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).

6.2.1 Neoadjuvant Therapy

Hormonal therapy is sometimes given for several months before radical therapy. 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.

Recommendation

- Neoadjuvant and concurrent LHRHa therapy for 3 to 6 months is recommended for men receiving radical radiotherapy for high-risk localised or locally advanced prostate cancer.

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

6.2.2 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.

Recommendation

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

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

Recommendations

- Adjuvant hormonal therapy for up to 3 years is recommended for men receiving neoadjuvant hormonal therapy and radical radiotherapy for locally advanced or high-risk localised prostate cancer who have a Gleason score of ≥8.
- Adjuvant hormonal therapy is not recommended for men with a Gleason score of ≤7.

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

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 (Tyrrell *et al.* 2005) suggests the survival benefit of adjuvant bicalutamide monotherapy is comparable.

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 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 suitable 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.

6.2.3 Hormonal Therapy Alone

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.

6.2.4 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 LHRHas. 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 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

6.3.1 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.

6.3.1.1 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.

Recommendation

- Pelvic radiotherapy should be considered in men with >15% risk (estimated using the Roach formula (%LN risk = 2/3 PSA + [10x (Gleason score - 6)]) of pelvic lymph node involvement who are to receive neoadjuvant hormonal therapy and radical radiotherapy to the prostate.

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

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 Guideline Development Group did not rate this topic as a health economic priority, therefore no attempt has been made to review or summarise the relevant cost-effectiveness literature.

6.3.1.2 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.

6.3.1.3 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

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

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

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.

Health Economic Evidence

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

6.3.2 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.

6.3.3 Other Local Therapies

Cryotherapy or HIFU are used in some centres for men with T2/3 disease as a primary treatment. Recommendations on the use of cryotherapy and HIFU can be found in Chapter 4.

Recommendations on the follow-up of men with localised prostate cancer can be found in Chapter 4. These recommendations also apply to men with locally advanced prostate cancer.

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.

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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 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 maximal androgen blockade. When bilateral orchidectomy or LHRHa monotherapy fails an anti-androgen may be added as second-line hormonal therapy.

Recommendation

- Bilateral orchidectomy should be recommended as an alternative to continuous LHRHa therapy.

Qualifying Statement: There are randomised studies which show comparable survival benefit and side effects for bilateral orchidectomy. A full systematic review of the published economic evaluations is currently in progress.

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.

Recommendation

- Combined androgen blockade is not recommended as first-line treatment.

Qualifying statement: Evidence shows only a modest survival benefit for combined androgen blockade and high costs.

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, but 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.

Recommendation

- For men 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[††††] is appropriate.

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

Recommendation

- Men taking bicalutamide who do not maintain satisfactory sexual function, should stop bicalutamide and be treated with androgen withdrawal.

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

7.5 Intermittent Androgen Withdrawal

The standard approach to hormonal therapy for metastatic prostate cancer 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 as an alternative to continuous androgen withdrawal, especially to men with severe side effects.

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

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

[††††] The BNF states that bicalutamide monotherapy should be at a dose of 150mg daily. A lower dose (50mg) is used for CAB.

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.

LHRHa's versus combined androgen blockade

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 an LHRH agonist alone withdrew from therapy at a rate of 4% or less compared with a rate of 8% or more in men receiving combined androgen blockade (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. One small randomised trial (de Leval *et al.* 2002) comparing intermittent with continuous androgen withdrawal reported that most patients experienced slight to moderate adverse effects, but these usually resolved in the intermittent androgen withdrawal group in the periods when the men were off treatment.

Health Economic Evaluation

A full systematic review of the published economic evaluations is currently in progress.

7.6 Interventions for Managing 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 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 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 (>6 months) bicalutamide monotherapy daily should receive prophylactic radiotherapy to both breast buds within the first month of treatment. A single fraction of 8Gy using orthovoltage radiotherapy is recommended.
- If radiotherapy is unsuccessful in preventing gynacomastia, weekly tamoxifen should be considered.
- Men starting androgen withdrawal therapy should be informed that regular resistance exercise reduces fatigue and improves quality of life.

Qualifying statement: These recommendations are based on GDG consensus, informed by several small randomised control trials (RCTs).

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 Guideline Development Group 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 maximal 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.

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: This recommendation is taken from the NICE Health Technology Assessment TA101 (NICE, 2006).

Recommendation

- When men develop biochemical evidence of hormone refractory disease their management options should be discussed by the urology 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.

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 (HRPC). 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, prednosolone 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

- Dexamethasone at a dose of 0.5mg daily‡‡‡‡ is recommended as third line hormonal therapy after androgen withdrawal and anti-androgen therapy.

Qualifying statement: 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 21–26% for prednisolone and 21.5% for hydrocortisone. There was no evidence, however, about the relative effect of different corticosteroids on survival.

Health Economic Evaluation

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

‡‡‡‡ Often used at higher doses in other indications.

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 is currently in development which may expand these recommendations.

Recommendation

- Men with hormone refractory prostate cancer shown to have extensive disease 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.

Recommendation

- 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.

Clinical Evidence

A prospective case series (Bayley *et al.* 2001) reported screening for sub-clinical spinal cord compression using MRI 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 (Venkitaraman et al 2007; Bayley *et al.* 2001), duration of hormonal therapy (Bayley *et al.* 2001) and back pain (Venkitaraman et al. 2007).

Health Economic Evaluation

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

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.

Recommendation

- The use of bisphosphonates to prevent or reduce the complications of bone metastases in men with HRPC 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.

Recommendation

- Bisphosphonates for pain relief may be considered when other treatments, including analgesics and palliative radiotherapy, have failed. The choice of drug should be based on the cost and either the oral or intravenous route of administration should be chosen according to convenience and tolerability.

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, and no conclusions could be drawn. 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.

Recommendations

- Bisphosphonates should not be used routinely in men receiving androgen withdrawal therapy for prostate cancer.
- The recommendations in the NICE Clinical Guideline on Osteoporosis should be followed once it is published.

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; Magno *et al.* 2005b; Nelson *et al.* 2006; 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 (Nelson *et al.* 2006; Smith *et al.* 2001; 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 delay or reduce the rate of development of bone metastases.

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.

Strontium-89 (Sr-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.

Recommendation

- Sr-89 should be considered for men with painful bone metastases from HRPC especially for 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 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 is effective for the control of pain from bony metastases but there was no evidence of an overall survival benefit for patients treated with strontium-89.

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 HRPC 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

7.12.1 Management of Obstructive Uropathy

Prostate cancer may result in unilateral or bilateral obstruction of the ureters resulting in impaired renal function.

The development of obstructive uropathy in men with hormone 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.

Recommendations

- Upper urinary tract decompression 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 openly with men and remains a choice for some.

Qualifying statement: This recommendation is based on observational evidence of effectiveness and GDG consensus.

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

7.12.2 Management of haematuria

Locally advanced prostate cancer can result in haematuria caused by bleeding from the prostatic urethra or base of bladder. Endoscopic control of bleeding points can be performed under general anaesthesia. Palliative radiotherapy to the bladder base and prostate also may be effective.

7.12.3 Management of bowel obstruction

Local extension of prostate cancer into the rectum can cause luminal narrowing or complete obstruction. The former can usually be managed by alterations to the diet, the prescription of aperiants and consideration of radiotherapy. Complete obstruction of the lower bowel may require a defunctioning colostomy.

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.

7.13.1 Multidisciplinary needs of men with prostate cancer

The present provision of palliative care to NHS patients involves substantial service provision in the independent and charitable sector as well as service within the NHS.

The management of physical symptoms and the psychological needs of men with metastatic prostate cancer needs to draw on the expertise of many clinical disciplines. 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, experts in pain as well as generic and specialist palliative care providers.

7.13.2 The Dying Patient

Some men will die from their prostate cancer but many will die from other diseases whilst they have prostate cancer. It is important to identify when men are close to death and ensure that symptom relief and palliative care is available to all. This may require generic or specialist palliative care.

The effective management of symptoms at the end of life, in all care settings, is supported by the use of appropriate care pathways. The Liverpool Care Pathway for the Dying (http://www.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 receive tailored information and access to specialist urology and palliative care teams to address their specific needs.
- The regular assessment of needs (described in the NICE Guidance on 'Improving supportive and palliative care for adults with cancer' (NICE 2004)) should be applied systematically to men with prostate cancer.
- Men with metastatic prostate cancer should be given the opportunity to discuss their therapy and information needs with members of both urology and specialist palliative care teams when there are significant changes in their disease status or symptoms.
- Palliative interventions at any stage should be integrated into co-ordinated care, and any transitions of care settings should be facilitated as smoothly as possible.
- Men with prostate cancer, their partners and carers should be consulted as early as possible in respect of their values and preferences for palliative care. Treatment/care plans and preferred place of care should be tailored accordingly.
- Palliative care should be available when needed and not limited to being available only at 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 Guideline Development Group 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.

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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 4ng/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 4ng/ml will have cancer, of which some will be clinically significant. As such, a cut-off of 4ng/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 2-10ng/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 2ng/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.

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Appendix 2

TNM Staging for Prostate Cancer[§§§§]

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

[§§§§] Sobin LH, Wittekind CH, editors (2002) *TNM classification of malignant tumours* 6th edition. New York: Wiley-Liss

STAGE	SUB-STAGE	DEFINITION
Node		**Regional lymph nodes**
	NX	Regional lymph nodes can not be assessed
	N0	No regional lymph nodes metastasis
	N1	Regional lymph node metastasis

1

STAGE	SUB-STAGE	DEFINITION
Metastasis		**Systemic spread**
	MX	Distant metastasis can not be assessed
	M0	No distant metastasis
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Metastasis at other site(s)

2

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 published economic literature relating to the choice of treatment strategy for men with clinically localised prostate cancer is extremely sparse. The systematic literature review identified 4 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 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 National Health Services (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.

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 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, 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'. 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.

The model's cycle length was yearly, 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 treatment 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 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)[†††††]

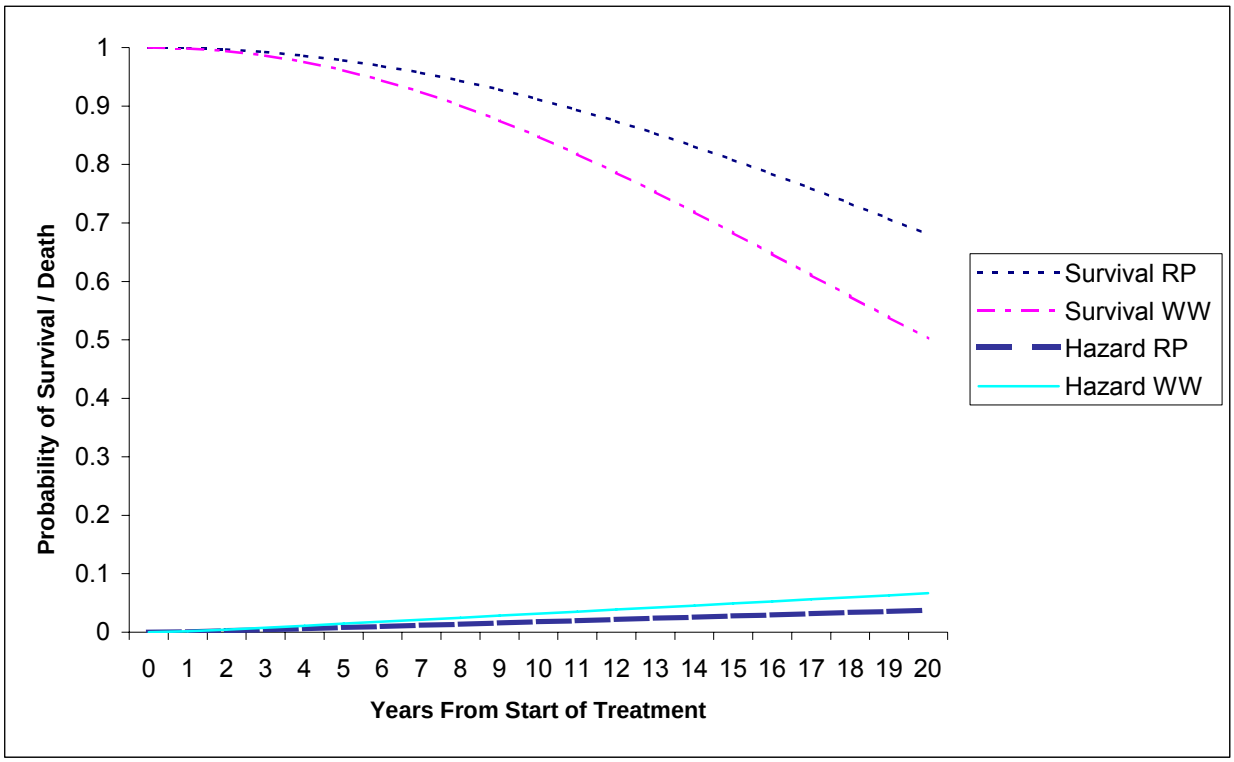
Transition Probabilities and Treatment Effects

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[‡‡‡‡‡] from the published 10-year Kaplan-Meier disease-specific survival curve (Figure 1). 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.

[†††††] The latter scenario was taken to represent the main baseline result.

[‡‡‡‡‡] A Weibull function is a mathematical method used to estimate the probability of an event happening over time given the observed data. In this instance, it has been used to estimate the probability of death each year.

Figure 1: Reported and extrapolated disease-specific survival curves and hazard functions derived from Bill-Axelson et al. (2005)



RP, Radical Prostatectomy; WW, Watchful Waiting

The survival curves are analogous to Kaplan-Meier survival curves. However, the hazard functions relate to the annual probability of death, which increases with increasing time. In both instances, the first 10-years relate to the observed data, whereas years 11-20 relate to the extrapolation

The effectiveness of radical prostatectomy was modelled by adjusting the baseline probabilities of death from prostate cancer and metastatic disease by the associated relative risks, as published in Bill-Axelson et al. (2005) 0.56 (95%CI 0.36-0.88) (Figure 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, 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 [6]. 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)[††††††].

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 person with localised disease, with impotence and urinary obstruction experienced a utility of 0.48 (0.78 – 0.09 – 0.21). Whereas, for a person 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 National Health Service'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 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 patients were assumed to receive a transurethral resection of the

[§§§§§] 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.

[******] 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.

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

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 1: Unit cost estimates

Cost	Estimate	Source
Radical Prostatectomy	£5603	Calvert et al. (2003)
Hormonal Treatment (annual)	£2612	Hummel et al. (2003)
Transurethral Resection (elective)	£2009	NHS Unit Costs [a]
Urinary Incontinence	£115 (per annum)	Turner et al. [b]
Twice yearly PSA test	£154	Calvert et al.(2003)
External Beam Radiotherapy (30 fractions)	£3600	NHS Unit Costs (@ £120 per fraction)
Two Phase Intensity Modulated Radiotherapy	£10000	Assumption
Brachytherapy	£6304	Hummel et al. (2003)
Cryotherapy	£7942	Hummel et al. (2003)]
HIFU	£12800	www.hifucancertreatment.co.uk

[a] One-off cost

[b] These costs relate to UK individuals with 'significant urinary storage problems', and are not prostate-cancer specific.

Where necessary, costs were inflated to 2006 prices using the Hospital and Community Health Services (HCHS) Pay and Prices Index.

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 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 incremental cost-effectiveness ratio (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.

[‡‡‡‡‡] 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.

Results

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

	Cost	LY	QALYs[1]	QALYs[2]
WW	£6185	9.69	6.96	6.63
RP	£10619	10.19	7.52	6.36
ICER		£8868	£7918	**Dominated**

RP, Radical Prostatectomy; WW, Watchful Waiting; ICER, incremental cost-effectiveness ratio
In QALYs[1], there is 0 probability of complications following treatment whereas in QALYs[2], 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. 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 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.

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 3). For example, external beam radiotherapy cost an additional £2431 than watchful waiting (£8616 - £6185), meaning that 0.08 QALYs are required to make it cost-effective compared to watchful waiting, over a 20 year period. For HIFU, the most costly option at £17816, the equivalent value was 0.39 QALYs, or an additional 4.3 months of perfect health over 20 years.

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

Treatment	Expected Cost of Treatment	Required QALY Increase[a]	Equivalent Health Gain In Months[b]
External beam	£8618	0.08	1
Brachytherapy	£11320	0.17	2
Cryotherapy	£12958	0.23	2.8
I	£15016	0.29	3.5
HIFU	£17816	0.36	4.3

[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 0.08 QALYs.

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 health-related quality-of-life (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 effective 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 the £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 0.08 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 HIFU, the most costly option, the equivalent figure was 4.3 months. Thus while the absence of randomised controlled trials 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 patients who develop progressive disease, the ability to accurately detect progressive disease and treatment efficacy in patients 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 health-related quality-of-life) 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.

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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 focussed ultrasound
HRPC	hormone refractory prostate cancer
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
PSA	prostate specific antigen
PSA-DT	prostate specific antigen doubling time
QALY	quality adjusted life years
RCT	randomised controlled trial
SRE	skeletal related event
SSRI	Selective Serotonin Reuptake Inhibitor
TRUS	trans-rectal ultrasound
TURP	trans-urethral resection of the prostate

Appendix 5

Glossary

Active surveillance: a method of managing low or intermediate-risk prostate cancer that aims to target radical treatment only to those cases that need it.
Adjuvant treatment: treatment given in addition to the main treatment.
Androgen withdrawal therapy: treatment that works by lowering testosterone levels. This can be achieved either by bilateral orchidectomy or with LHRH agonists.
Anti-androgen drugs: drugs that act by binding to and blocking the hormone receptors of cancer cells, thereby preventing androgens from stimulating the cancer.
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.
Bone scan: a scan intended to show any abnormal areas of bone.
Bowel toxicity: symptoms caused by treatment-related damage to the bowel.
Brachytherapy: is a form of radiotherapy given by inserting radio-active seeds directly into the prostate.
CAB: Combined Androgen Blockade.
***Clinically detected disease*:** cancer that came to light as a result of a symptom or abnormal clinical finding.
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.
***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).
External beam radiotherapy (EBRT): 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.
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 (≤7) indicates a relatively favourable cancer, a high Gleason score (≥) indicates a relatively aggressive cancer.
Grading: the degree of malignancy of a tumour, judged by its appearance under the microscope.
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 treatment/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.

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.

Isotope bone scintigraphy: another name for a bone scan.

Karnofsky status: classifies patients according to their functional impairment.

LHRHa (Luteinising hormone-releasing hormone agonists): hormonal drugs that inhibit the production of androgens from the testes.

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).

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.

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

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.

Multi Disciplinary Team (MDT): a team with members from different health care professions (e.g. urology, oncology, pathology, radiology, nursing).

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.

Palliative: anything which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it.

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.

***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 (PIN): 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.

Prostate Specific Antigen (PSA) test: a test which measures PSA levels in the blood.

Radical treatment: treatment given with the aim of cure, rather than just improving symptoms.

Retropubic prostatectomy: a technique where the prostate is removed through an incision in the abdomen.

Salvage therapy: treatment that is given after the cancer has progressed following other treatments.

***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.

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.

Transrectal ultrasound: 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.

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 the disease of those who are not suitable for radical treatment, involving palliative treatment only if and when they develop symptoms.

Appendix 6

Guideline Scope

1. Guideline title

Prostate cancer: diagnosis and treatment

1.1 Short title

Prostate cancer

2. Background

(a) 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.

(b) 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.

(c) 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).

(d) 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.

3. Clinical need for the guideline

Prostate cancer is one of the commonest cancers in men. Each year there are about 27,773 new cases in England and Wales[a] [b] and 9161 deaths[c]. Prostate cancer is

[a] Office for National Statistics, Cancer Statistics Registrations: Registrations of cancer diagnosed in 2001, England. Series MB1 no. 32. 2004, National Statistics: London.
[b] Welsh Cancer Intelligence and Surveillance Unit, 2003.
[c] Office for National Statistics, Mortality Statistics: Cause. England and Wales 2003. TSO: London.

predominantly a disease of older men but around 20% of cases occur in men under the age of 65. Over the past 10 to 15 years there have been a number of significant advances in its management but also a number of major controversies, especially about the clinical management of patients with early, non-metastatic disease. These uncertainties clearly cause anxieties for patients and their families. There is evidence of practice variation around the country and of patchy availability of certain treatments and procedures. A clinical guideline will help to address these issues and offer guidance on best practice.

4. The guideline

a) 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.

b) 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).

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

4.1 Population

4.1.1 Groups that will be covered

a) 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).

b) 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.)

c) No patient subgroups needing special consideration have been identified.

4.1.2 Groups that will not be covered

a) Asymptomatic adults with an abnormal, age-specific PSA level and no biopsy-proven diagnosis of prostate cancer.

b) Patients with metastatic disease of different primary origin involving the prostate.

c) Children and adults with rare malignant tumours of the prostate, such as small cell carcinoma and rhabdomyosarcoma.

4.2 Healthcare setting

a) Primary care – excluding population-based and opportunistic screening.

b) Secondary care.

c) Tertiary care by specialist urological cancer teams.

4.3 Clinical management

a) Investigation to establish a histopathological diagnosis.

b) Diagnostic investigations for clinical staging.

c) Active surveillance of men with localised disease suitable for radical treatment.

d) Surgical management including radical prostatectomy, perineal prostatectomy, laparoscopic prostatectomy, high-frequency ultrasound, radiofrequency ablation and cryotherapy.

e) Radiotherapy including external beam, brachytherapy (high and low dose rate) and unsealed radioactive sources (strontium-89 and samarium-153).

f) Hormonal treatments: neo-adjuvant, adjuvant and palliative; surgical and pharmacological.

g) Cytotoxic chemotherapy: neo-adjuvant, adjuvant and palliative.

h) Bisphosphonates.

i) Novel biological and immunological agents.

j) The management of common treatment-related side effects and complications.

k) Patient information, support and specific aids for complex decision making.

4.4 Status

4.4.1 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.

Related published NICE guidance

- National Institute for Health and Clinical Excellence (2005). Referral guidelines for suspected cancer. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/CG027

- National Institute for Clinical Excellence (2002). Improving outcomes in urological cancers. London: National Institute for Clinical Excellence. Available from www.nice.org.uk/csguc

- National Institute for Clinical Excellence (2004). Improving supportive and palliative care for adults with cancer. London: National Institute for Clinical Excellence. Available from www.nice.org.uk/csgsp

4.4.2 Guideline

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

5. 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.

6. 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 Patient Centred Care

- 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 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, EBRT, brachytherapy, conformal radiotherapy, conventional radiotherapy, HIFU, 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 intervention 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 therapy 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 therapy 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?
- 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 compression, does routine MRI scan of 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 HRPC 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 refractory 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

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

Conflicts of Interests

The Guideline Development Group were asked to declare any possible conflicts of interest and none that could interfere with their work on the guideline.

Mark Baker (Chair):
Conducted work (for fees) for industry intermediaries who are reimbursed by pharmaceutical companies, specifically Roche and Pfizer. Does not have direct contact with the healthcare industry bodies. Declared 7 May 07

John Graham (Lead Clinician):
Lecture Fees, accommodation and travel expenses received from Astra Zeneca Pharmaceuticals, Aventis, Sanofi-Aventis and Bayer Pharmaceuticals. Involved in Industry sponsored clinical trials for Astellas Pharmaceuticals, Boehringer Ingelheim, Immunicon, Cell Genesys Inc., Sanofi-Aventis, GPC Pharmaceuticals, Sonus Pharmaceuticals, Glaxo SmithKline, PDL Inc. Consultancy Fees from Pfizer. Clinical trial work with Bayer Pharmaceuticals. Declared February 06 and July 07

Angela Billington:
Consultancy on writing leaflets and articles on incontinence issues. Working group on incontinence issues. Both for pharmaceutical companies. Declared October 05

David Gillatt:
Sponsorship for meeting from Astra Zeneca. Educational and research grants from Astra Zeneca. Sponsorship from Sanofi Aventis to go to the European Society of Urological Oncology meeting. Expenses paid by EDAP to observe and trained on the Ablatherm HIFU machine. Looking for sponsorship for annual meeting (BAUS Section of Oncology). Declared October 05 and July 07

Brendan Carey
Sponsorship for lecturing and mentoring from Oncura IBT. Declared July 07

Chris Hiley:
Occasionally accepts fees from pharmaceutical companies for involvement in particular activities, but these fees go to the charity worked for not personally. Charity worked for both receives and solicits funding from pharmaceutical companies, but personally has no connections with these negotiations and is usually unaware of the presence of financial support or details. Declared September 05

Chris Parker:
Astra Zeneca, Algeta, Sanofi Aventis, Cell Genesys, Link Pharmaceuticals – received honoraria for giving presentations or attending Advisory boards. Consultant to Algeta. Declared September 05, February 06, April 06, May and July 07

John Rawlinson:
Has contact with but no contractual relationship with a range of healthcare providers and organisations in the field of mental health but none related to prostate disorders. Declared September 05

John Wiles:
Chairman and executive committee member of the Association for Palliative Medicine of Great Britain and Ireland. Medical Director Harris HospisCare. Trustee of the National Council for Palliative Care. Declared November 05

Jervoise Andreyev:
Has received an unrestricted educational grant from Norgine which was used to run an ongoing study investigating the optimal treatment of radiotherapy-induced faecal incontinence. Also has an ongoing project funded by an unrestricted educational grant from SHS International which is investigating the use of elemental diet in preventing acute and hence long term toxicity. Has submitted or have in late stages of preparation 5 grant applications looking at different aspects of radiation-induced gastrointestinal damage. Declared December 06

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
- Cancer Services Collaborative Improvement Partnership
- CancerBACUP
- CASPE
- Cephalon UK Ltd
- Chartered Society of Physiotherapy
- Clatterbridge Centre for Oncology NHS Trust
- College of Occupational Therapists

Coloplast Ltd

Commission for Social Care Inspection

Connecting for Health

Continence Foundation

Cornwall & Isles of Scilly PCt

Countess of Chester Hospitals NHS Trust

Craven, Harrogate & Rural District PCT

DakoCytomation Ltd

David Lewis Centre, The

Denbighshire Local Health Board

Department of Health

EDAP-TMS

Eisai Ltd

Faculty of Public Health

Ferring Pharmaceuticals Ltd

General Practice and Primary Care

Gloucestershire Hospitals NHS Trust

Guerbet Laboratories Ltd

Guildford & Waverley PCT

Healthcare Commission

Help the Hospices

Independent Healthcare Advisory Service

Intra-Tech Healthcare Ltd

Ipsen Ltd

James Whale Fund for Kidney Cancer

Johnson & Johnson Medical

King's College Hospital NHS Trust

King George's Hospital NHS Trust

Leeds North East PCT

Leeds Teaching Hospitals NHS Trust

Link Pharmaceuticals

Liverpool PCT

Long Term Medical Conditions Alliance

Luton and Dunstable Hospital NHS Trust

Macmillan Cancer Relief

Maidstone and Tunbridge Wells NHS Trust

Medical Research Council Clinical Trials Unit

Medicines and Healthcare Products Regulatory Agency

Medway NHS Trust, The

Men's Health Forum

MERCK SHARP & DOHME

National Audit Office

National Association of Assistants in Surgical Practice

National Cancer Network Clinical Directors Group

National Cancer Research Institute (NCRI) Clinical Studies Group

National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)

National Council for Palliative Care

National Kidney Research Fund

National Osteoporosis Society

National Patient Safety Agency

National Public Health Service – Wales

NCCHTA

NHS Cancer Screening Programme

NHS Direct

NHS Health and Social Care Information Centre

NHS Quality Improvement Scotland

North East London Strategic Health Authority

North Eastern Derbyshire PCT

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

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 Cancer Charity, The

Prostate Cancer Research Foundation, The

PSA Prostate Cancer Support Association

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

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 East Sheffield PCT

South West Kent PCT

Staffordshire Moorlans PCT

Stockport PCT

Tameside and Glossop PCT

Taunton Road Medical Centre

Thames Valley Strategic Health Authority

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

Walsall Teaching PCT

Wareney PCT

Welsh Assembly Government

Wessex Cancer Trust

West Cornwall PCT

West Lincolnshire PCT

Western Cheshire PCT

Whipps Cross University Hospital NHS Trust

Wirral Hospital NHS Trust

World Cancer Research Fund International

Wyeth Pharmaceuticals

Yamanouchi Pharma Ltd

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*[1]	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff
Victoria Titshall*[2]	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
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*[3]	Lecturer in Health Economics, London School of Health and Tropical Medicine
Dr Dyfrig Hughes*[4]	Director, Centre for the Economics and Policy in Health, University of Wales, Bangor
Dr Rhiannon Tudor*[4]	Director, Centre for the Economics and Policy in Health, University of Wales, Bangor
Pat Link*[4]	Research Officer, Centre for the Economics and Policy in Health, University of Wales, Bangor
Eugenia Priedane*[4]	Research Fellow, 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

Needs Assessment

Dr Sean McPhail*[3]	Head of Cancer Analysis, Cancer Intelligence Service South West Public Health Observatory
Dr Tanya Cross*[4]	South West Public Health Observatory

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)

Debra Collard
Lay representative

Jonathan Hopper
Medical Director (UK and Ireland), ConvaTec