Prostate cancer: diagnosis and treatment

Update of clinical guideline 58

Appendix J: Sections from NICE clinical guideline 58 (2008) that have been removed

Appendix K: Recommendations from NICE clinical guideline 58 (2008) that have been deleted or changed

Appendix L: Sections from NICE clinical guideline 58 (2008) Evidence Review that have been removed

Appendix M: Section from the NICE version where recommendations have been deleted or changed

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Appendix J - Sections from NICE clinical guideline 58 (2008) that have been removed

Key priorities

1. Healthcare professionals should adequately inform men with prostate cancer and their partners or carers about the effects of prostate cancer and the treatment options on their sexual function, physical appearance, continence and other aspects of masculinity. Healthcare professionals should support men and their partners or carers in making treatment decisions, taking into account the effects on quality of life as well as survival.

2. To help men decide whether to have a prostate biopsy, healthcare professionals should discuss with them their prostate specific antigen (PSA) level, digital rectal examination (DRE) findings (including an estimate of prostate size) and comorbidities, together with their risk factors (including increasing age and black African and Caribbean ethnicity) and any history of a previous negative prostate biopsy. The serum PSA level alone should not automatically lead to a prostate biopsy.

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

4. Men undergoing radical external beam radiotherapy for localised prostate cancer1 should receive a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction.

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

6. Healthcare professionals should ensure that men with troublesome urinary symptoms after treatment have access to specialist continence services for assessment, diagnosis and conservative treatment. This may include coping strategies, along with pelvic floor muscle re-education, bladder retraining and pharmacotherapy.

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

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

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

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

11. Healthcare professionals should ensure that palliative care is available when needed and is not limited to the end of life. It should not be restricted to being associated with hospice care.

Key research recommendations

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

The greatest uncertainties in managing prostate cancer are around the identification of which cancers are of clinical significance and over the choice of radical treatment, and in which settings they are appropriate.

With the diagnosis of prostate cancer being made more frequently in asymptomatic men, it is of growing importance to know which of these men are likely to benefit from aggressive treatment.

2. **Research is required into the clinical and cost effectiveness of treatments aimed at the elimination of disease in men with localised prostate cancer, with locally advanced disease and with locally recurrent disease. This research should include a rigorous examination of the value of procedures such as brachytherapy (localised disease only), cryotherapy and high intensity focused ultrasound, as well as combinations of surgery and radiotherapy with hormonal therapy and chemotherapy. The endpoints should include survival, local recurrence, toxicity and quality of life outcomes.**

A wide and growing range of radical therapies aimed at the eradication of disease are available. Although long-term follow-up data are available for some of these in the localised disease setting, there have been no randomised trials comparing these treatments and there is little evidence to support their use in locally advanced disease or localised recurrent disease.

Methodology

Introduction

What is a Clinical Guideline?

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

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

Who is the Guideline Intended For?

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

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

The Remit of the Guideline

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

'To prepare a guideline for the NHS in England and Wales[1] for the clinical management of prostate cancer, to supplement existing service guidance. The guideline should cover:

- the key diagnostic and staging procedures – excluding screening
- the main treatment modalities including hormonal therapy (covering surgical and chemical castration)
- The role of tumour specific bisphosphonates

[1] Since this remit was received, clinical guidelines now apply to Northern Ireland.

What the Guideline Covers - The Scope

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

- provide an overview of what the guideline would include and exclude
- identify the key aspects of care that must be included
- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C and the remit
- inform the development of the clinical questions and search strategy
- inform professionals and the public about the expected content of the guideline.

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

Involvement of Stakeholders

Key to the development of all NICE guidelines are the relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2007). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the prostate cancer guideline can be found in Appendix 8.

Needs Assessment

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

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

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

The Process of Guideline Development – Who Develops the Guideline?

Overview

The development of this guideline was based upon methods outlined by the 'NICE guidelines manual'. A team of health professionals, lay representatives and technical experts known as the GDG (see Appendix 8), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, defined the scope which sets the parameters of the guideline
- Forming the guideline development group
- developing clinical questions
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

The Guideline Development Group (GDG)

The prostate cancer GDG was recruited in line with the existing NICE protocol as set out in the 'NICE guidelines manual'. The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were informally interviewed prior to being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Requests for nominations were sent to the main stakeholder organisations and patient organisations/charities (see Appendix 8). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms, following nomination from their respective stakeholder organisation. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix 8).

Guideline Development Group Meetings

Thirteen GDG meetings were held between 10 November 2005 and 28 June 2007. During each GDG meeting (either held over one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

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

Patient/Carer Representatives

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

Expert Advisers

During the development phase of the guideline the GDG identified areas where there was a requirement for expert input on particular specialist clinical questions. The clinical questions were addressed by either the production of a position paper or a formal presentation by a recognised expert who had been identified via the relevant registered stakeholder organisation.

A full list of recognised experts who contributed to the guideline can be found in Appendix 8. All relevant position papers are presented as part of the evidence review and will also appear on the accompanying CD-ROM to this guideline.

Developing Clinical Evidence-Based Questions

Background

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

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

Clinical guidelines should be aimed at changing clinical practice and should avoid ending up as ‘evidence-based textbooks’ or making recommendations on topics where there is already agreed clinical practice. It was therefore felt important that the 30 clinical questions should be prioritised into areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

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

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

Questionnaires were subsequently sent to the Prostate Cancer Advisory Groups of all 37 cancer networks in England and Wales with a request for a 4-week turnaround. (A list of all cancer networks can be found on the Cancer Action Team website at the DH).

Questionnaires were also sent via the Patient and Public Involvement Programme (PPIP) at NICE to all relevant patient/carer stakeholder organisations.

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

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

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

Care Pathway

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

Review of Clinical Literature

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions. Additionally, stakeholder organisations were invited to submit evidence for consideration by the GDG, provided it was relevant to the agreed list of clinical questions.

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

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

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1994 onwards
- Psychinfo 1806 onwards
- Web of Science 1970 onwards. [specifically Science Citation Index Expanded
- (SCI-EXPANDED) and Social Sciences Citation Index (SSCI)]
- System for Information on Grey Literature In Europe (SIGLE) 1980–2005
- Biomed Central 1997 onwards

- National Research Register (NRR)
- Current Controlled Trials.

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

Searches were updated and re-run 6–8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, 1 June 2007 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review (and will also appear on the accompanying CD-ROM to this guideline).

Critical Appraisal and Evidence Grading

Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. The researcher then individually applied the inclusion/exclusion criteria to determine which studies would be relevant for inclusion and subsequent appraisal. Lists of excluded papers were generated for each question and the rationale for the exclusion was presented to the GDG when required.

The researcher then critically appraised the full papers. Critical appraisal checklists were compiled for each paper and one researcher undertook the critical appraisal and data extraction.

The reviewer assessed the quality of eligible studies by referring to the SIGN quality checklist for systematic reviews/meta-analyses and randomised control trials (Table B). Evidence relating to clinical effectiveness was classified using this established hierarchical system. However this checklist is less appropriate for studies reporting diagnostic tests of accuracy. In the absence of a validated hierarchy for this type of test, NICE suggests levels of evidence that take into account the factors likely to affect the validity of these studies.

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

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

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

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

In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

Incorporating Health Economics Evidence

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

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

In order to assess the cost-effectiveness of each priority topic, a comprehensive systematic review of the economic literature was conducted. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics and quality of life filter.

Each search strategy was designed to find any applied study estimating the cost or cost effectiveness of the topic under consideration. A health economist reviewed abstracts and relevant papers were ordered for appraisal.

Published economic evidence was obtained from a variety of sources:

- Medline 1966 onwards
- Embase 1980 onwards
- NHS Economic Evaluations Database (NHS EED)
- EconLit 1969 onwards.

Economic Modelling

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

Overall Relevance of the Topic

- The number of patients affected: interventions affecting relatively large numbers of patients were given a higher economic priority than those affecting fewer patients

- The health benefits to the patient: interventions that 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.

Agreeing the Recommendations

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

Qualifying Statements

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

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

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

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

Consultation and Validation of the Guideline

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

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

Following the consultation period the GDG finalised the recommendations and the NCC-C produced the final document. This was then submitted to NICE for approval and publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other Versions of the Guideline

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

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

- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations the Quick Reference Guide (QRG), which is a summary of the main recommendations in the NICE guideline. This is available in hard copy via the NHS telephone response line (0870 1555 455)
- Understanding NICE Guidance (UNG), which describes the guideline using non-technical language. It is written chiefly for men with prostate cancer but may also be useful for family members, advocates or those who care for men with prostate cancer. This is available in hard copy via the NHS telephone response line (0870 1555 455).

Updating the Guideline

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

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

Funding

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

Disclaimer

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

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

References

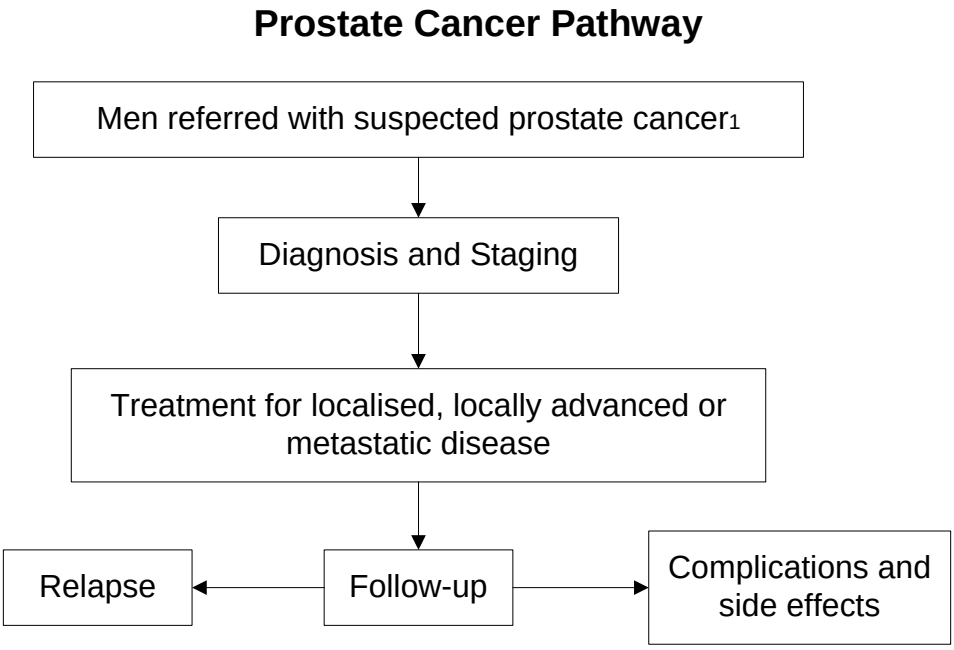
National Institute for Health and Clinical Excellence (2005) The guidelines manual. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence (2006) The guidelines manual. London: National Institute for Health and Clinical Excellence.

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

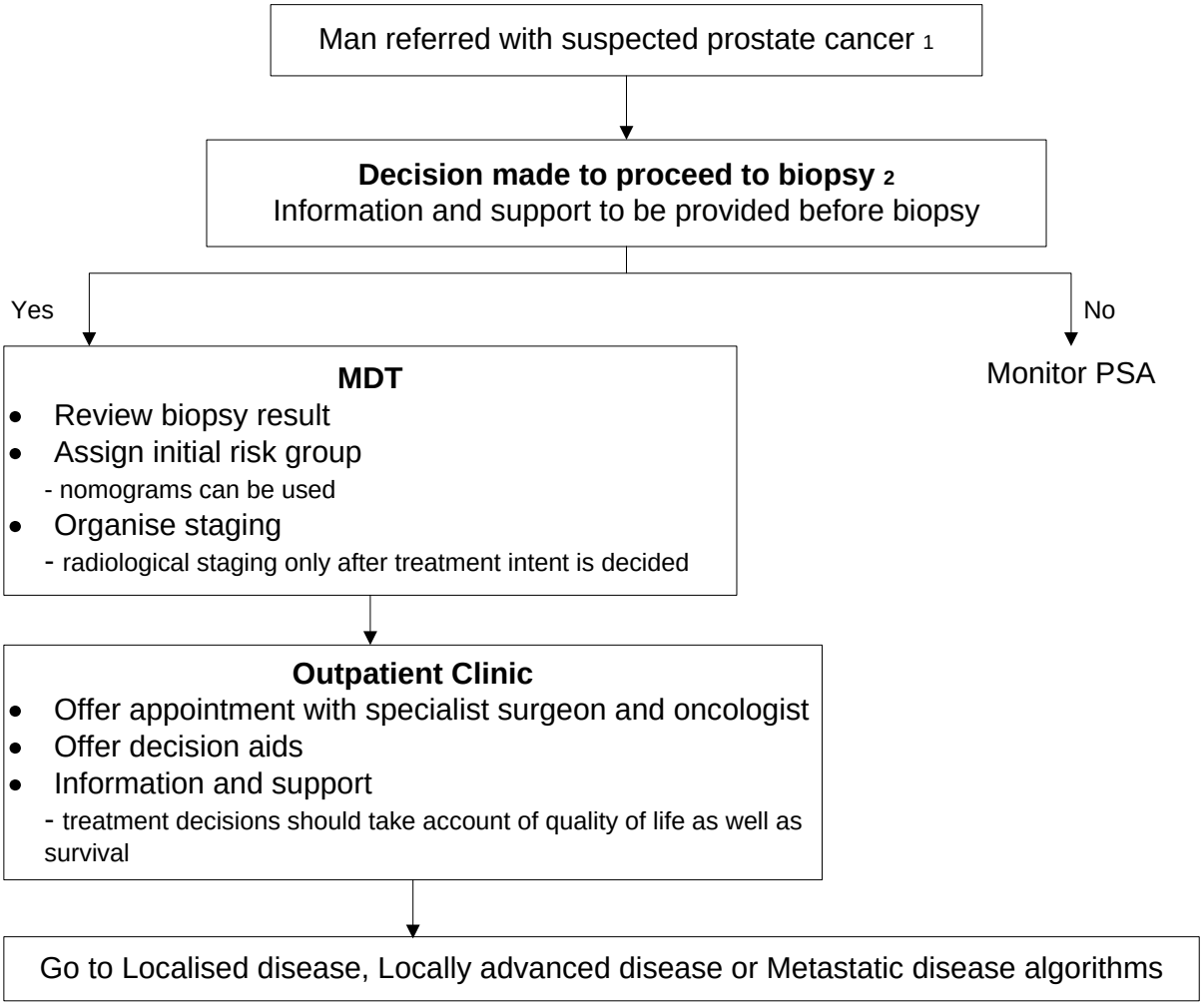
Algorithms

A pictorial guide to show how the guideline is structure.



[1] Referral guidelines for suspected cancer. NICE clinical guideline (2005)

Diagnosis and Staging



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

Localised Disease

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

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

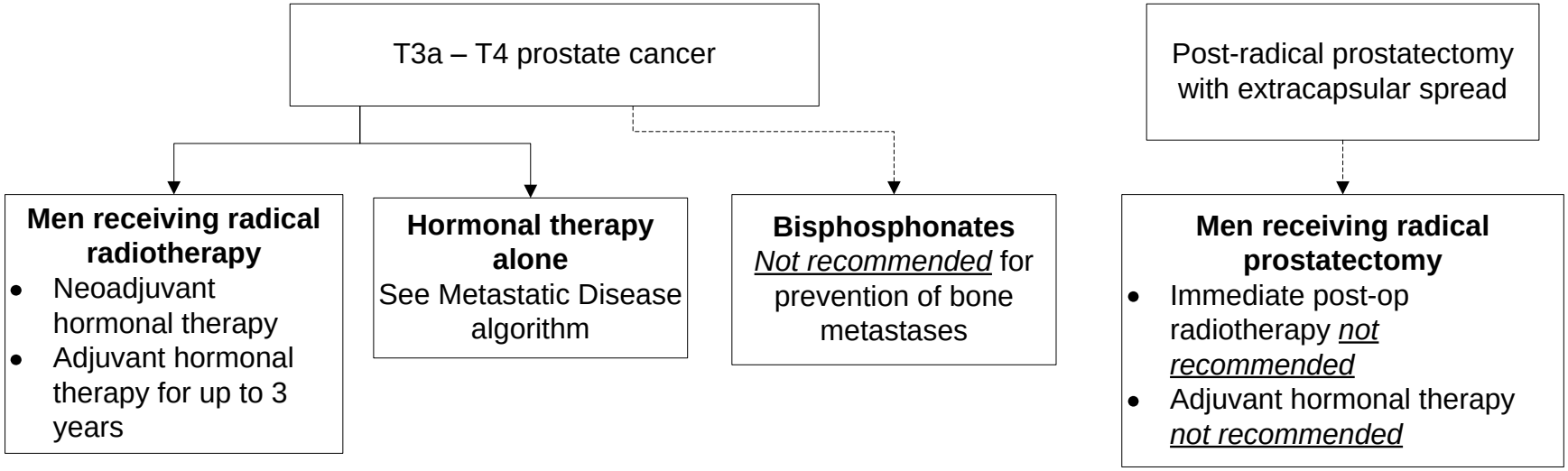
- Use conformal radiotherapy
- Minimum dose 74Gy

	Low-risk men (PSA ≤ 10 ng/ml and Gleason score ≤ 6 and T1-T2a)	Intermediate risk men (PSA 10-20 ng/ml or Gleason score 7 or T2b-c)	High-risk men (PSA ≥ 20 ng/ml or Gleason score ≥ 8 or T3-T4)
Watchful waiting	◇	◇	◇
Active surveillance	✓	◇	X
Brachytherapy	◇	◇	X
Radical prostatectomy	◇	✓	✓
Radical radiotherapy	◇	✓	✓
Cryotherapy	X*	X*	X*
HIFU	X*	X*	X*

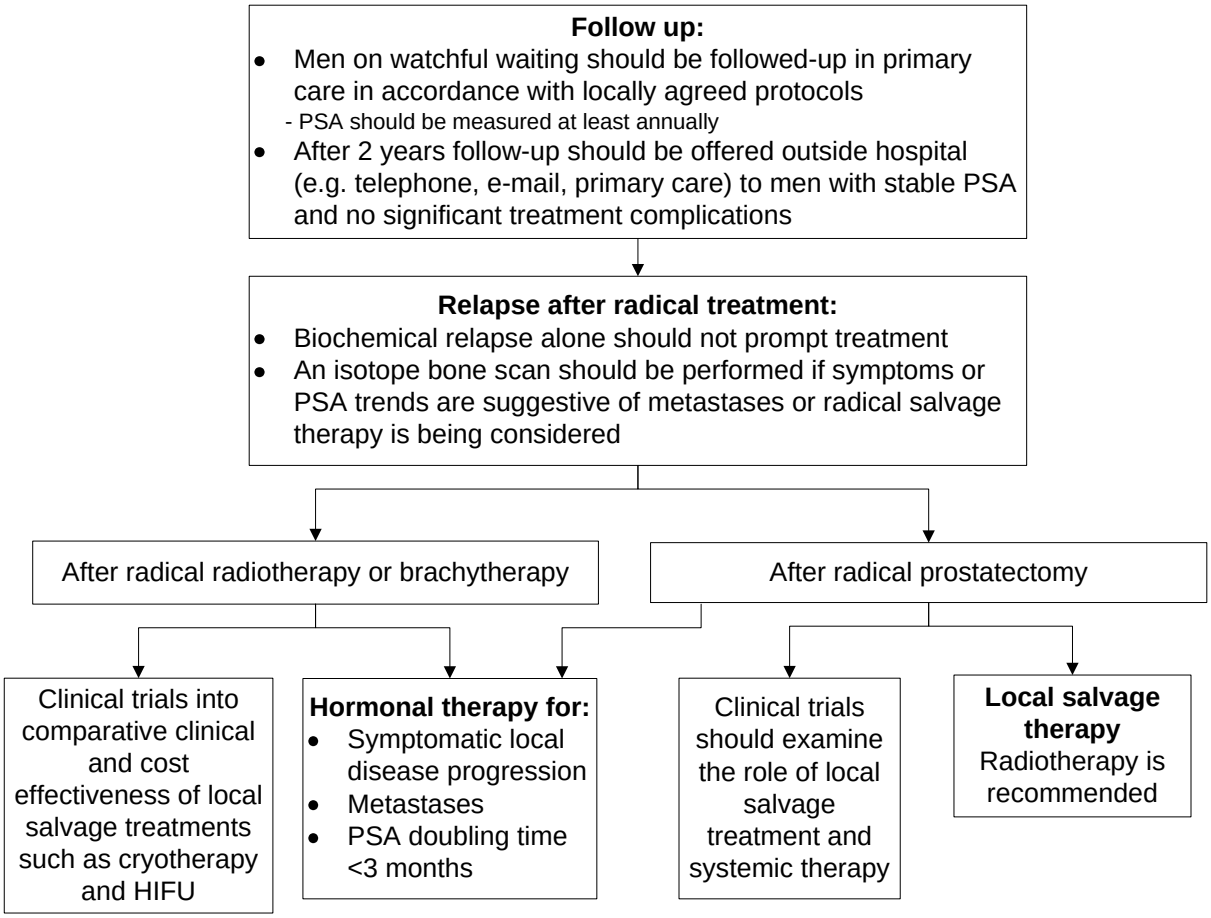
✓	Preferred treatment
◇	Treatment option
X	Not recommended
X*	Not recommended other than in the context of clinical trials

Locally Advanced Disease

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

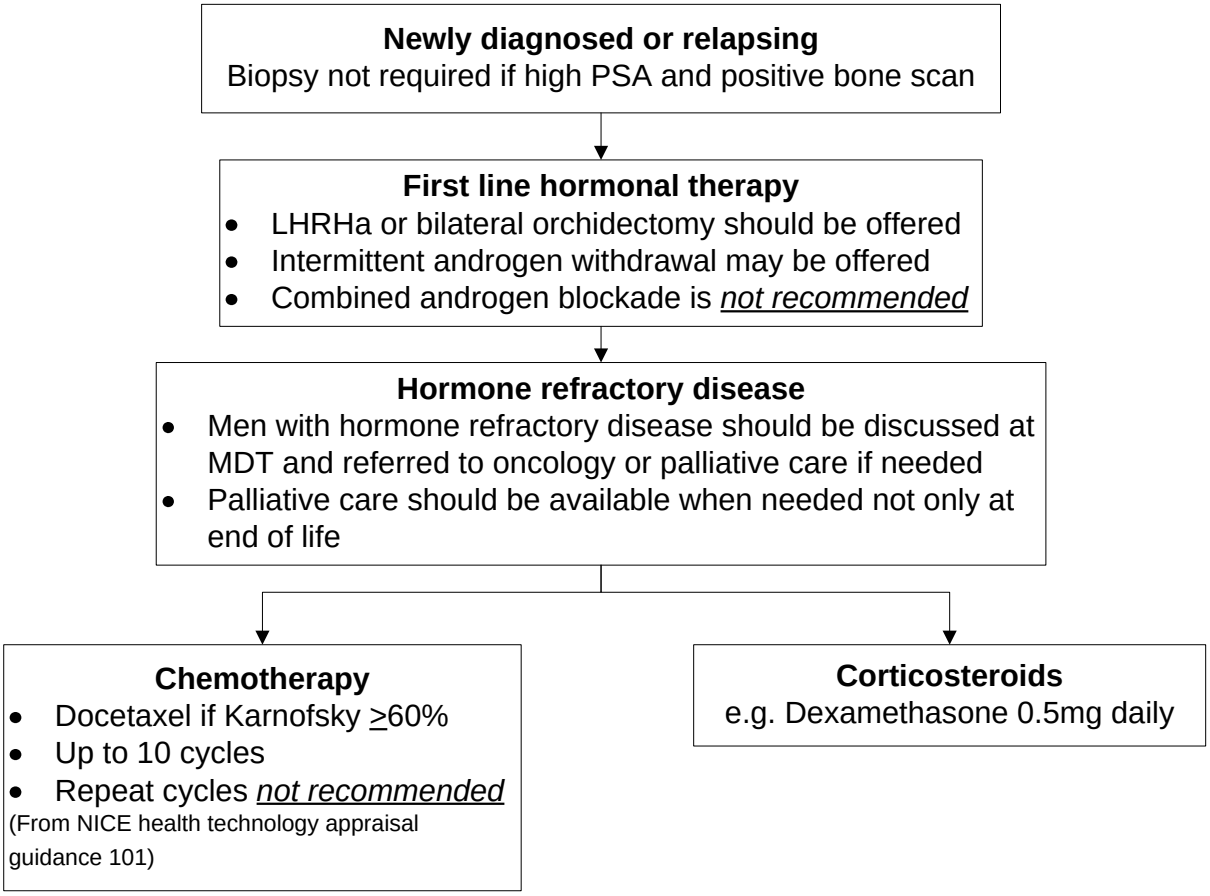


Follow-up and Relapse after Radical Treatment

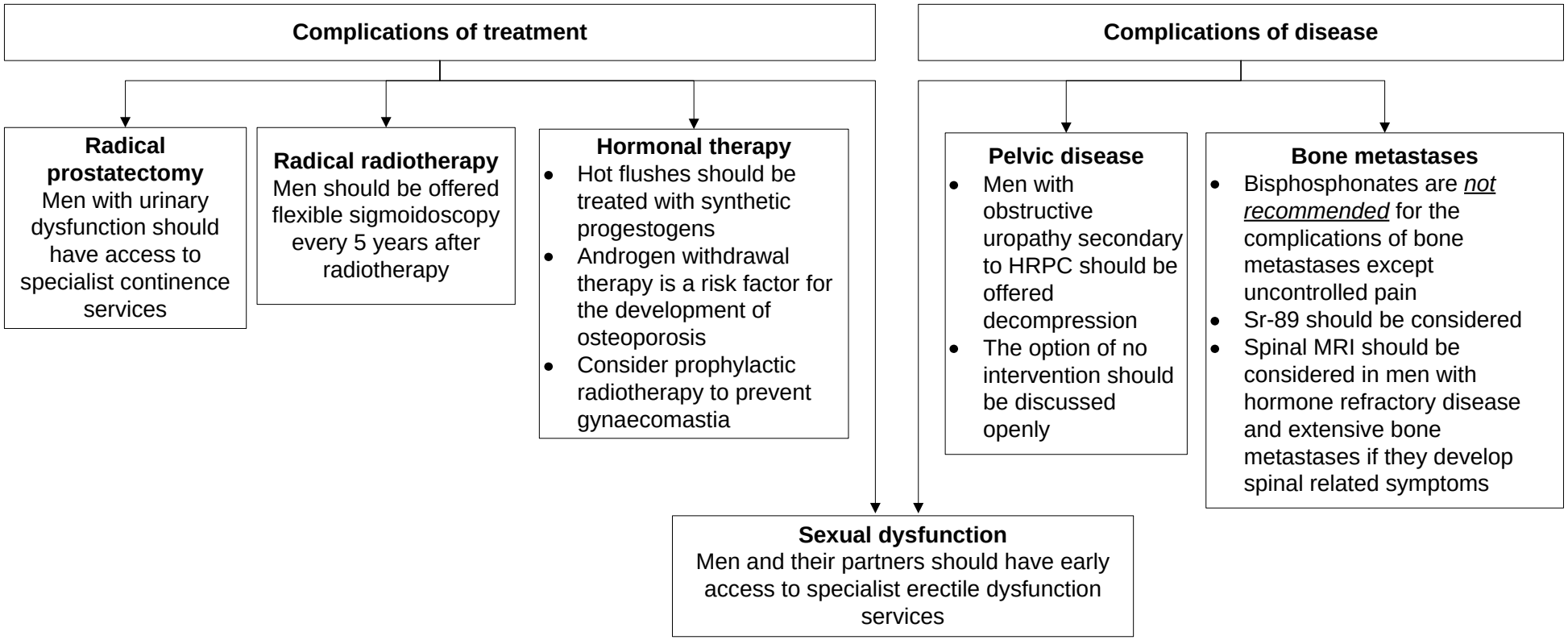


Metastatic Disease

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



Management of Complications and Side Effects of Treatment



1 Epidemiology

1.1 Introduction

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

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

1.2 Incidence

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

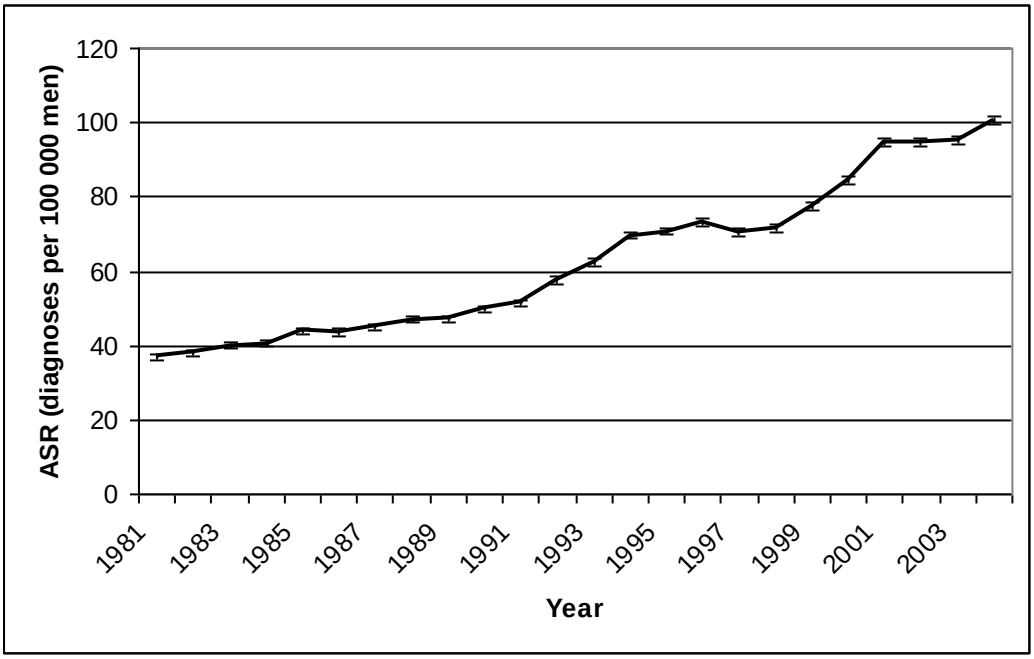


Figure 1.1 Directly Age Standardised Rate (ASR) of prostate cancer incidence in England and Wales (to European standard population). Data source: Office of National Statistics MB1 series and Welsh Cancer Intelligence unit and Surveillance (WCISU).

Between 1996 and 2004 the age standardised incidence rate of prostate cancer increased in all cancer networks in England and Wales[2]. 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.

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

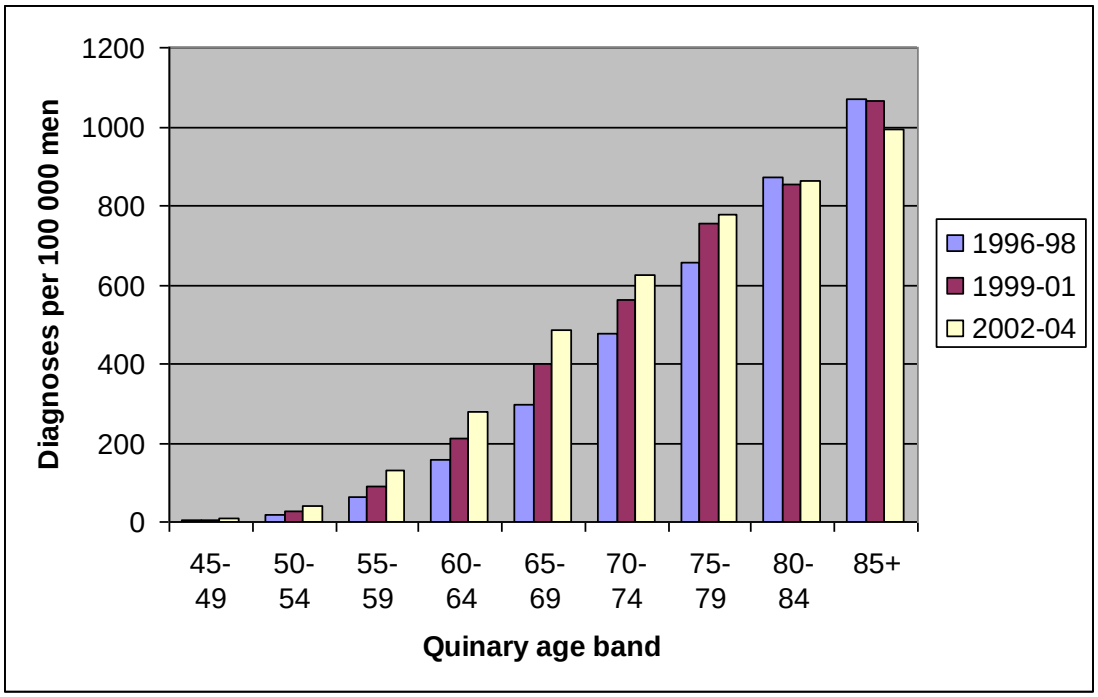


Figure 1.2 Rate of diagnosis of prostate cancer by 5-year age band. Data source: cancer registries of England and Wales.

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).

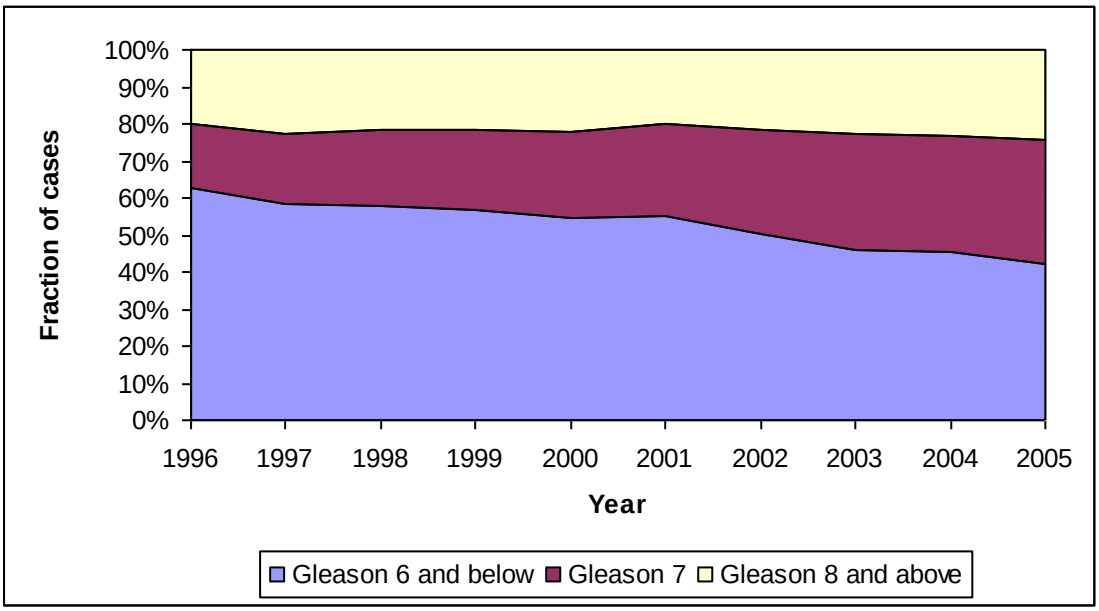


Figure 1.3 Stacked plot of prostate cancer diagnoses broken down by Gleason score (where the score is recorded) for the South West of England. Data source: British Association of Urological Surgeons registry database and South West Public Health Observatory.

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 prostate specific antigen (PSA) testing among affluent men[3].

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

1.3 Mortality

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

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

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

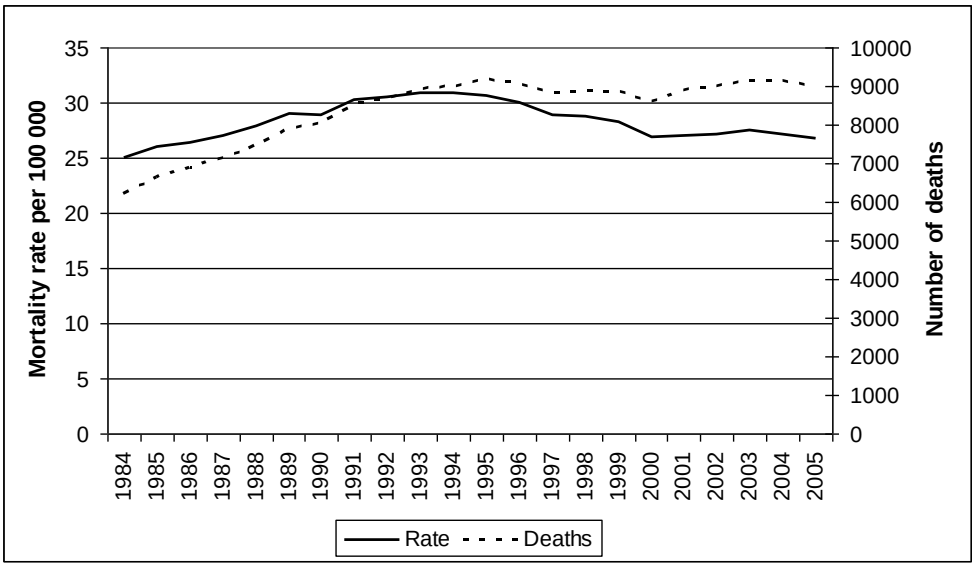


Figure 1.4 Directly Age Standardised mortality Rate (to European Standard population) and number of deaths from prostate cancer in England and Wales 1984 –2005. Data source: Office of National Statistics.

There is a variation in mortality across cancer networks in England and Wales during the period of decline in national mortality rate, although there is no consistent regional variation[4].

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

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

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

[4] Data Source: Office of National Statistics and Ordnance Survey

communication June 2007) show that prostate cancer mortality varies significantly by race. Prostate cancer mortality is higher in black men than white men, driven by the markedly higher incidence. The fatality ratio however is not significantly different.

1.4 Survival

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

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

1.5 Diagnosis and Investigations

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

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

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

1.6 Surgery

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

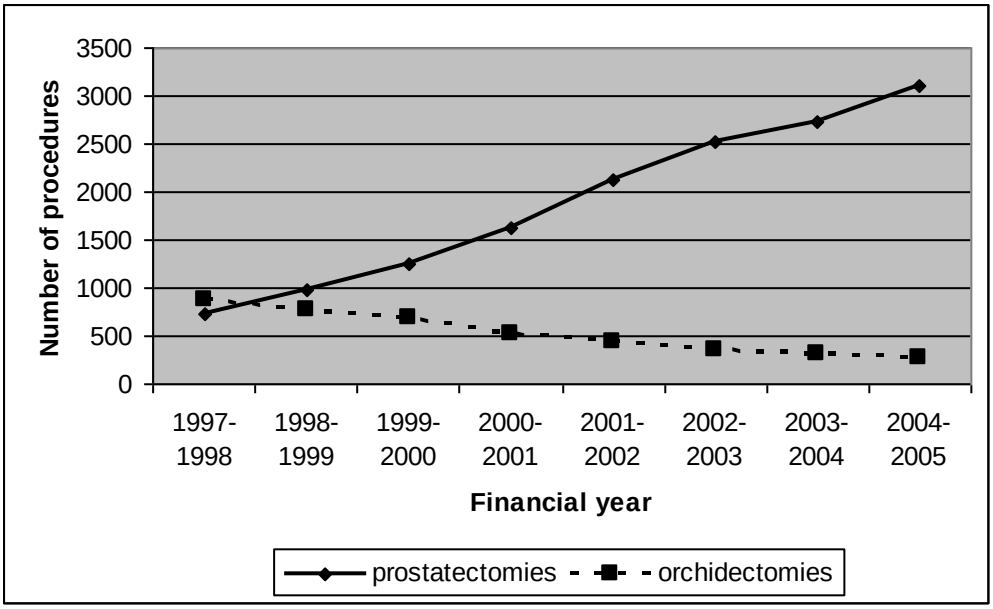


Figure 1.5 Numbers of all radical prostatectomy and orchidectomy operations on prostate cancer patients in England. Prostatectomies defined by OPCS code M61, Orchidectomies are defined by OPCS codes N05 and N06. Data source: HES data provided by NATCanSAT.

Metastatic prostate cancer can be treated by the surgical removal of the testes, otherwise known as orchidectomy (Cancer Research UK). This suppresses the level of testosterone in the body and retards the growth of prostate tumours. Surgical orchidectomy is becoming a less common way of treating prostate cancer (see Figure 1.5). From 1997–98 to 2003–04 the number of operations which took place on men with metastatic prostate cancer reduced by 75%. Medical castration, using hormonal therapy, has replaced orchidectomy in most cases.

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

The majority of prostatectomies recorded on the British Association of Urological Surgeons (BAUS) cancer registry are performed on men with a Gleason score of 6 or 7 (i.e. lower grade tumours)[5]. 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.

[5] Data source: BAUS cancer registry

1.7 Hormonal Therapy

Hormonal therapy prescriptions have increased dramatically since the mid-1980s[6]. 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[7]. Clear differences in the patterns of dose and fractionation occur across NHS trusts, indicating a variation in practice[8].

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%). 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).

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[6] Data Source: IMS Health Medical Data Index, London

[7] Data Source: South West Public Health Observatory and RES dataset provided by NatCanSAT

[8] Data Source: RES data provided by NATCanSAT

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

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

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3 Diagnosis and staging of prostate cancer

3.1 When to biopsy

, as set out in the referral guidelines for suspected cancer (NICE clinical guideline 27, 2005).

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

The aim of prostate biopsy is not to detect each and every prostate cancer. After all, the PCPT demonstrates that the majority of prostate cancers are in men with a normal PSA level.

, around 50% (Draisma et al. 2003)

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

3.2 Histological diagnosis

, or holmium laser resection of the prostate (HoLeP).

, commissioned a review which

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.

3.3 Staging classification for prostate cancer

Imaging at the time of diagnosis for prostate cancer

Low-risk PSA < 10 ng/ml and Gleason score ≤ 6 and clinical stage T1-T2a

Intermediate-risk PSA 10–20 ng/ml, or Gleason score 7, or clinical stage T2b or T2c

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

Imaging for T-staging and N-staging

, typically with endorectal coil imaging at 1.5 Tesla

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.

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

Health economic evaluation (2008)

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

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

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

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

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4 Localised prostate cancer

4.2 Predictive factors and risk groups

Low-risk PSA < 10 ng/ml and Gleason score ≤ 6 and clinical stage T1-T2a

Intermediate-risk PSA 10–20 ng/ml, or Gleason score 7, or clinical stage T2b or T2c

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

4.3 Treatment decision making

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

4.4 Initial treatment options

Active surveillance

The objective of active surveillance is to avoid unnecessary treatment of men with indolent cancers, by only treating those whose cancers show early signs of progression. Whereas traditional watchful waiting in elderly or infirm men aims to avoid any treatment at all for as long as possible and excludes radical treatment options, active surveillance of younger, fitter men tries to target curative treatment on those likely to benefit. Active surveillance enables the risk category to be re-assessed at regular intervals by serial PSA estimations, and transrectal ultrasound (TRUS) guided prostate biopsy. Active surveillance is an option for men with low-risk disease who are fit for radical treatment in the event of disease progression.

Clinical evidence (2008)

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

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

Health economic evaluation (2008)

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 (2008)

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

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

Health economic evaluation (2008)
The literature search on the indications for stopping active surveillance identified 53 potentially relevant papers, but none were obtained for appraisal as they did not include any economic evaluations. No economic modelling was attempted because there was considered to be insufficient clinical information on which to base a model.

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

External beam radiotherapy

There is currently a variety of dose-fractionation regimens in use in England and Wales.

Brachytherapy

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

4.5 Managing adverse effects of treatment

Rectal problems after radiotherapy

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 be due to treatable causes or intercurrent pathology. There is an increased risk of rectal cancer after pelvic radiation but faecal occult blood testing is a poor discriminator due to telangiectasis and the emerging National Screening Programme for bowel cancer is inappropriate for these men.

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

There is an increased risk of rectal cancer after pelvic radiation but faecal occult blood testing is a poor discriminator due to telangiectasis and the emerging National Screening Programme for bowel cancer is inappropriate for these men.

Clinical evidence

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

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

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

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

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

Health economic evaluation

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

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6 Locally advanced prostate cancer

6.1 Introduction

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

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

Neoadjuvant therapy

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

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

Adjuvant therapy

The duration of hormonal therapy has ranged from 6 months to indefinite.

Clinical evidence (2008)

Adjuvant therapy with radical radiotherapy

Evidence about neoadjuvant and adjuvant hormonal therapy comes from a systematic review (Kumar et al. 2006) of 21 randomised controlled trials.

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.

Other adjuvant therapies

Bisphosphonates are also used in the treatment of age-related osteoporosis and, since osteoporosis is a side effect of androgen withdrawal therapy, bisphosphonates have been studied as a preventive measure in men who are starting long-term hormonal therapy with LHRHa's.

6.3 Local Management of locally advanced prostate cancer

Radiotherapy

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

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

Lymph node involvement
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.

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.

7 Metastatic prostate cancer

7.5 Intermittent androgen withdrawal

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

Clinical evidence (2008)
The literature search identified no reliable evidence about the impact of intermittent androgen withdrawal on survival. In their systematic review of five small randomised trials, Conti and co-workers (Conti et al. 2007) concluded that the available information suggests that intermittent androgen deprivation therapy may have a slightly reduced risk of adverse events when compared with continuous androgen deprivation.

7.6 Managing the complications of hormonal therapy

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

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

Clinical evidence (2008)
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.

7.8 Chemotherapy

Men with poor performance status who may not tolerate docetaxel are usually treated with the combination of mitoxantrone and prednisolone.

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.

7.11 Bone targeted therapies

or as treatment for the osteoporosis caused by hormonal therapy.

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

Appendix 2: TNM Staging for Prostate Cancer[9]

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

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

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)

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

Appendix 5: Glossary

Bone scan
A scan intended to show any abnormal areas of bone.

Enteropathy
Disease of the intestines.

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.

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

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

Appendix 7: List of topics covered by each chapter

Chapter 2 – Communication and Support

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

Chapter 3 – Diagnosis and staging of prostate cancer

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

Chapter 4 – Localised prostate cancer

- In men with localised prostate cancer what are the risk factors for:
  - Disease specific mortality
  - Lymph node involvement
  - Treatment failure (disease recurrence, biochemical relapse)?
- In men with localised or locally advanced prostate cancer, which treatments (radical prostatectomy, external beam readiotherapy, brachytherapy, conformal radiotherapy, conventional radiotherapy, high intensity focused ultrasound, cryotherapy) are clinically and cost effective compared to watchful waiting?
- In men with prostate cancer, who is eligible to receive active surveillance and what is the most effective protocol to follow?
- In men with prostate cancer receiving active surveillance, what are the indicators for 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 treatment and how should biochemical relapse be defined?
- In men with biochemical relapse following radical treatment for prostate cancer, what staging investigations are effective?
- In men with biochemical relapse following radical treatment for prostate cancer, what salvage therapies for local recurrence are effective?

Chapter 6 – Locally advanced prostate cancer

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

Chapter 7 – Metastatic prostate cancer

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

Appendix K - Recommendations from NICE clinical guideline 58 (2008) that have been deleted or changed

Recommendations to be deleted

The table shows recommendations from 2008 that NICE proposes deleting in the 2014 update. The right-hand column gives the replacement recommendation, or explains the reason for the deletion if there is no replacement recommendation.

Recommendation in 2008 guideline	Comment
Men should decide whether or not to have a re-biopsy following a negative biopsy, having had the risks and benefits explained to them. [1.2.6]	Replaced by: Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound 10–12 core biopsy to determine whether another biopsy is needed. [1.2.7] and Do not offer another biopsy if the multiparametric MRI (usingT2- and diffusion-weighted imaging) is negative, unless any of the risk factors listed in recommendation 1.2.6 are present. [1.2.8]
Men with high-risk localised and locally advanced prostate cancer who are being considered for radical treatment should have pelvic imaging with either magnetic resonance imaging (MRI), or CT if MRI is contraindicated. [1.2.10]	Replaced by: Consider multiparametric MRI, or CT if MRI is contraindicated, for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. [1.2.12]
Magnetic resonance spectroscopy is not recommended for men with prostate cancer except in the context of a clinical trial. [1.2.11]	Replaced by: Consider multiparametric MRI, or CT if MRI is contraindicated, for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. [1.2.12]
Men with low-risk localised prostate cancer who are considered suitable for radical treatment should first be offered active surveillance. [1.3.3] Active surveillance is particularly suitable for a subgroup of men with low-risk localised prostate cancer who have clinical stage T1c, a Gleason score 3+3, a PSA density < 0.15 ng/ml/ml and who have cancer in less than 50% of their total number of biopsy cores with < 10mm of any core involved. [1.3.4]	Replaced by: Offer active surveillance as an option to men with low-risk localised prostate cancer for whom radical surgery or radiotherapy is suitable. [1.3.5] and Ensure that men: • are told about treatment options and their risks and benefits **and** • are aware that there is limited evidence for some treatment options **and** • are not unduly influenced by healthcare professional preference when selecting treatment options. [1.1.13]
To reduce the sampling error associated with prostate biopsy, men who are candidates for active	Consider using the following protocol for men who have chosen active surveillance:

<table>
<tr>
<td>surveillance should have at least 10 biopsy cores taken. [1.3.7]

Active surveillance should include at least one re-biopsy and may be performed in accordance with the ProSTART protocol. [1.3.8]</td>
<td>
<table>
<tr><th>Timing</th><th>Tests[a]</th></tr>
<tr><td>At enrolment in active surveillance</td><td>MultiparametricMRI if not previously performed</td></tr>
<tr><td>Year 1 of active surveillance</td><td>Every 3–4 months: measure PSA[b]
Throughout active surveillance: monitor PSA kinetics[c]
Every 6–12 months: DRE[d]
At 12 months: prostate rebiopsy</td></tr>
<tr><td>Years 2–4 of active surveillance</td><td>Every 3–6 months: measure PSA[b]
Throughout active surveillance: monitor PSA kinetics[c]
Every 6–12 months: DRE[d]</td></tr>
<tr><td>Year 5 and every year thereafter until active surveillance ends</td><td>Every 6 months: measure PSA[b]
Throughout active surveillance: monitor PSA kinetics[c]
Every 12 months: DRE[d]</td></tr>
<tr><td colspan="2">a If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or re-biopsy
b May be carried out in primary care if there are agreed shared-care protocols and recall systems.
c May include PSA doubling time and velocity
d Should be performed by a healthcare professional with expertise and confidence in performing DRE</td></tr>
</table>
[1.3.6]
</td>
</tr>
<tr><td>Active surveillance should be discussed as an option with men who have intermediate-risk localised prostate cancer. [1.3.5]</td><td>Consider active surveillance for men with intermediate-risk localised prostate cancer who do not wish to have immediate radical treatment.In line with recommendation 1.3.6 [1.3.21]</td></tr>
<tr><td>Adjuvant hormonal therapy is recommended for a minimum of 2 years in men receiving radical radiotherapy for localised prostate cancer who have a Gleason score of ≥ 8. [1.3.1.6]</td><td>This recommendation was a repeat of a recommendation in the Locally Advanced Prostate Cancer chapter of the guideline. In accordance with NICE style it has been replaced by a cross reference.</td></tr>
<tr><td>Men treated with radical radiotherapy for prostate cancer should be offered flexible sigmoidoscopy every 5 years. [1.4.3]</td><td>This recommendation has been deleted because a review of the evidence did not support retaining it.</td></tr>
<tr><td>Steroid enemas should not be used for treating men</td><td>A review of the evidence showed uncertainty of the effectiveness of steroid enemas rather than a lack of</td></tr>
</table>

with radiation proctopathy. [1.4.4]	effectiveness. Therefore, the disinvestment recommendation could not be retained.
Neoadjuvant and concurrent luteinising hormone-releasing hormone agonist (LHRHa) therapy is recommended for 3 to 6 months in men receiving radical radiotherapy for locally advanced prostate cancer. [1.6.1] and Adjuvant hormonal therapy is recommended for a minimum of 2 years in men receiving radical radiotherapy for locally advanced prostate cancer who have a Gleason score of ≥ 8. [1.6.3]	Replaced by: Offer men with intermediate- and high-risk localised prostate cancer 6 months of androgen deprivation therapy given before, during or after radical external beam radiotherapy. [1.3.16] and Consider extending the period of androgen deprivation therapy to 3 years for men with high-risk localised prostate cancer and discuss the benefits and risks of this option with them. [1.3.24]
Intermittent androgen withdrawal may be offered to men with metastatic prostate cancer providing they are informed that there is no long-term evidence of its effectiveness. [1.7.5]	Replaced by: Consider intermittent therapy for men having long-term androgen deprivation therapy (not in the adjuvant setting), and include discussion with the man, and his family or carers if he wishes, about: • the rationale for intermittent therapy **and** • the limited evidence for reduction in side effects from intermittent therapy **and** • the effect of intermittent therapy on progression of prostate cancer. [1.5.1] and For men who are having intermittent androgen deprivation therapy: • measure PSA every 3 months **and** • restart androgen deprivation therapy if PSA is 10 ng/ml or above, or if there is symptomatic progression. [1.5.2]
Synthetic progestogens (administered orally or parenterally) are recommended as first-line therapy for the management of troublesome hot flushes. If	Replaced by: Offer medroxyprogesterone[10] (20 mg per day), initially for 10 weeks, to manage troublesome hot flushes caused by long-term androgen suppression and evaluate the effect at the end of the treatment period. [1.5.3]

[10] At the time of publication (January 2014), medroxyprogesterone did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

oral therapy is used, it should be given for 2 weeks, and re-started, if effective, on recurrence of symptoms. [1.7.6]	and Consider cyproterone acetate or megestrol acetate[11] (20mg twice a day for 4 weeks) to manage troublesome hot flushes if medroxyprogesterone is not effective or not tolerated. [1.5.4] and Tell men that there is no good-quality evidence for the use of complementary therapies to treat troublesome hot flushes. [1.5.5]
Inform men starting androgen withdrawal therapy that regular resistance exercise reduced fatigue and improves quality of life. [1.7.9]	Replaced by: Tell men who are starting androgen deprivation therapy that fatigue is a recognised side effect of this therapy and not necessarily a result of prostate cancer. [1.5.18] And Offer men who are starting or having androgen deprivation therapy supervised resistance and aerobic exercise at least twice a week for 12 weeks to reduce fatigue and improve quality of life. [1.5.19]

Amended recommendation wording (change to meaning)

Recommendations are labelled **[2008, amended 2014]** if the evidence has not been reviewed but changes have been made to the recommendation wording (indicated by highlighted text) that change the meaning.

[11] At the time of publication (January 2014), megestrol acetate did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

Recommendation in 2008 guideline	Recommendation in current guideline	Reason for change
The results of all prostate biopsies should be reviewed by a urological cancer MDT. Men should only be re-biopsied following a negative biopsy after an MDT review of the risk characteristics including life expectancy, PSA, DRE and prostate volume. [1.2.5]	The results of all prostate biopsies should be reviewed by a urological cancer MDT. If a biopsy is negative, rebiopsy should be offered only after an MDT review of the man's risk factors. [1.2.5]	The text ' including life expectancy, PSA, DRE and prostate volume' has been deleted because it is now inconsistent with the protocol recommended for active surveillance.
Men with localised prostate cancer who have chosen an active surveillance regimen and who have evidence of disease progression (that is, a rise in PSA level or adverse findings on biopsy) should be offered radical treatment.[1.3.9]	Offer radical treatment to men with localised prostate cancer who have chosen an active surveillance regimen and who have evidence of disease progression. [1.3.22]	The text 'that is, a rise in PSA level or adverse findings on biopsy' has been deleted because it is now inconsistent with the protocol recommended for active surveillance.
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. [1.4.6]	Prior to radical treatment, warn men and, if they wish, their partner, that radical treatment for prostate cancer will result in an alteration of sexual experience, and may result in loss of sexual function. [1.3.9]	The original wording has been amended to clarify that partners are covered by the recommendation only if the man wishes this to be the case. Wording has also been amended to clarify this recommendation relates to radical treatment.
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. [1.4.7]	Warn men and, if they wish, their partner, about the potential loss of ejaculation and fertility associated with radical treatment for prostate cancer. Offer sperm storage. [1.3.10]	The original wording has been amended to clarify that partners are covered by the recommendation only if the man wishes this to be the case. Wording has also been amended to clarify this recommendation relates to radical treatment.
Men undergoing treatment for prostate cancer should be warned of the likely effects of the treatment on their urinary	Warn men undergoing radical treatment for prostate cancer of the likely effects of the treatment on their urinary	Wording has also been amended to clarify this recommendation

function. [1.4.12]	function. [1.3.11]	relates to radical treatment.
Healthcare professionals should ensure that men and their partners have early and ongoing access to specialist erectile dysfunction services. [1.4.8]	Ensure that men have early and ongoing access to specialist erectile dysfunction services. [1.3.34]	The text 'and their partners' has been deleted as this only applies to the man.

Changes to recommendation wording for clarification only (no change to meaning)

Recommendation numbers in current guideline	Comment
All recommendations except those labelled **[new 2014].**	Minor editorial changes have been made to these recommendations to reword them in the active form, in line with current NICE style for recommendations in clinical guidelines. Yellow shading has not been applied to these changes.
1.1.3 Offer men with prostate cancer advice on how to access information and support from websites, local and national cancer information services, and from cancer support groups.	The reference to UK Prostate Link has been deleted as the content of this website is no longer updated.
1.2.1 To help men decide whether to have a prostate biopsy, discuss with them their prostate-specific antigen (PSA) level, digital rectal examination (DRE) findings (including an estimate of prostate size) and comorbidities, together with their risk factors (including increasing age and black African or black Caribbean ethnicity) and any history of a previous negative prostate biopsy. Do not automatically offer a prostate biopsy on the basis of serum PSA level alone. [2008]	The abbreviations (PSA and DRE) have been written out in full in accordance with latest NICE style.
1.2.10 Do not routinely offer imaging to men who are not candidates for radical treatment.	The phrase 'in whom no radical treatment is intended' previously included in this recommendation would preclude patients on active surveillance from having imaging (as they may not ever have radical treatment). Therefore the wording has been changed to "who are not candidates for radical treatment" for clarity.
1.3.7 Offer radical prostatectomy or radical radiotherapy to men with intermediate-risk localised prostate cancer.	The word 'conformal' has been deleted because it is an outdated term
1.3.19 For men with localised prostate cancer[12] receiving radical external beam radiotherapy with curative intent, offer planned treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage.	The word 'conformal' has been deleted because it is an outdated term. It has been replaced by the phrase 'offer planned treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage'.
1.3.26 Do not offer brachytherapy alone to	The word 'alone' has been inserted to clarify this recommendation relates to

[12] This may also apply to some men with locally advanced prostate cancer.

men with high-risk localised prostate cancer.	brachytherapy alone.
1.3.27 Offer radical prostatectomy or radical radiotherapy to men with high-risk localised prostate cancer when there is a realistic prospect of long-term disease control.	The word 'conformal' has been deleted because it is an outdated term.
1.4.6 Begin androgen deprivation therapy and stop bicalutamide treatment in men with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function.	Amended to use current term 'androgen deprivation therapy'.
1.4.7 When men with prostate cancer develop biochemical evidence of hormone-relapsed disease, their treatment options should be discussed by the urological cancer MDT with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate.	Amended to use current term 'hormone-relapsed prostate cancer'.
1.4.11 Offer a corticosteroid such as dexamethasone (0.5 mg daily) as third-line hormonal therapy after androgen deprivation therapy and anti-androgen therapy to men with hormone-relapsed prostate cancer.	Amended to use current terms 'androgen deprivation therapy' and 'hormone-relapsed prostate cancer'.
1.4.12 Offer spinal MRI to men with hormone-relapsed prostate cancer shown to have extensive metastases in the spine (for example, on a bone scan) if they develop any spinal-related symptoms.	Amended to use current term 'hormone-relapsed prostate cancer'.
1.4.13 Do not routinely offer spinal MRI to all men with hormone-relapsed prostate cancer and known bone metastases.	Amended to use current term 'hormone-relapsed prostate cancer'.
1.4.15 Bisphosphonates for pain relief may be considered for men with hormone-relapsed prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed. Choose the oral or intravenous route of administration according to convenience, tolerability and cost.	Amended to use current term 'hormone-relapsed prostate cancer'.

1.4.16 Strontium-89 should be considered for men with hormone-relapsed prostate cancer and painful bone metastases, especially those men who are unlikely to receive myelosuppressive chemotherapy.	Amended to use current term 'hormone-relapsed prostate cancer'.
1.4.17 Offer decompression of the upper urinary tract by percutaneous nephrostomy or by insertion of a double J stent to men with obstructive uropathy secondary to hormone-relapsed prostate cancer.	Amended to use current term 'hormone-relapsed prostate cancer'.
1.4.18 The option of no intervention should also be discussed with men with obstructive uropathy secondary to hormone-relapsed prostate cancer and remains a choice for some.	Amended to use current term 'hormone-relapsed prostate cancer'.
1.5.12 Do not routinely offer bisphosphonates to prevent osteoporosis in men with prostate cancer having androgen deprivation therapy.	Amended to use current term 'androgen deprivation therapy'.

Appendix L - Sections from NICE clinical guideline 58 (2008) Evidence Review that have been removed

3 Diagnosis and staging

3.2 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?

Short Summary

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

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men referred with suspected prostate cancer whose initial biopsy is negative.	Follow-up investigations: ▪ An increased biopsy number per session using an 'extended biopsy template'. ▪ DRE examination ▪ PSA density ▪ PSA velocity ▪ f/t PSA ratio	▪ No follow up ▪ Comparisons between follow-up regimes: ▪ PSA, free versus total PSA ratio, ▪ re-biopsy techniques and detection rates, ▪ Frequency of investigations	▪ Accuracy of diagnosis of prostate cancer ▪ Morbidity associated with repeated investigations ▪ Morbidity associated with misdiagnosis

(The search strategy developed from this PICO table and used to search the literature for this question is in Appendix C)

Evidence summary

Cancer detection rate at repeat biopsy

Cancer detection rate at initial and repeat biopsy depends on the prevalence of prostate cancer, the biopsy technique used (Eichler *et al.* 2006) and the criteria for repeat biopsy (see section 3.2.1, figure 3.2.1.2). In three series reporting serial biopsies using mainly sextant biopsy (Aus *et al.* 2004; Lopez-Corona *et al.* 2003; Roehl *et al.* 2002), 25 to 30% of prostate cancers were discovered on repeat biopsy. In a small series (Mian *et al.* 2002), reporting serial repeat extended multi-site (10 or 11 core) biopsies only 5% of cancers were detected on repeat biopsy.

Optimal number of repeat biopsy sessions

- **Sensitivity.** Biopsy sensitivity for prostate cancer is increased by repeating biopsy in those with negative biopsy (see section 3.2.1 below). The optimal number of repeat biopsy sessions is a trade-off between biopsy sensitivity and the number of unnecessary biopsies The number of biopsy sessions per case of prostate cancer detected can be calculated (see section 3.2.1) if certain assumptions are made.
- **Specificity**. Repeating biopsy only in those with negative biopsy would decrease the specificity of biopsy. There is also the possibility that repeating biopsies will increase the detection rate of insignificant cancer.

Predictive factors for positive repeat biopsy (univariate analyses)

Only the factors in the PICO question were examined in detail.

- **PSA density (PSAD) and transition zone PSA density (PSA-TZD).** PSAD (Djavan *et al.* 2000; Eggener *et al.* 2005; Keetch *et al.* 1996) and PSA-TZD (Djavan *et al.* 2000; Singh *et al.* 2004) showed moderate ability to discriminate between those who did and did not go on to have positive repeat biopsy (see figure 3.2.1). The cut-off values used ranged from 0.05 and 0.15 ng/ml/cc for PSAD and between 0.19 and 0.26 ng/ml/cc for PSA-TZD**.** Djavan and co-workers (Djavan *et al.* 2000) examined both variables and found significantly better area under the ROC curve for PSA-TZD than for PSAD.
- **PSA velocity (PSAV).** PSAV appeared to have moderate sensitivity and specificity for the prediction of positive repeat biopsy (Eggener *et al.* 2005; Keetch *et al.* 1996; Lopez-Corona *et al.* 2003) (see figure 3.2.2) The range of cut-off values reported was 0 to 0.93 ng/ml/year although the reported sensitivity and specificity did not vary much in this range.
- **Percent free PSA (F/T-PSA RATIO).** The reported cut-off values of F/T-PSA RATIO ranged from 5% to 40% (Catalona *et al.* 1997; Djavan *et al.* 2000; Eggener *et al.* 2005; Fowler *et al.* 2000; Letran 1998; Singh *et al.* 2004). Visual inspection of the ROC curve (see figure 3.2.3) suggests moderate discriminative ability. After comparing ROC curves, Djavan and co-workers (Djavan *et al.* 2000) reported that F/T-PSA ratio was significantly better predictor of repeat biopsy results than other PSA measures (total PSA, PSA-TZD and PSAD)
- **Digital rectal examination (DRE).** Abnormal DRE did not appear to indicate those who would or would not go on to have a positive repeat biopsy (Fowler *et al.* 2000; Eggener *et al.* 2005; Keetch *et al.* 1996; Roobol *et al.* 2004; Singh *et al.* 2004; Lopez-Corona *et al.* 2003) (see figure 3.2.4).
- **Histology of initial biopsy.** In a series of 6380 men who had repeat biopsy after an initial (usually sextant) biopsy negative for prostate cancer, repeat biopsy was positive for prostate cancer in 26% of cases (O'Dowd *et al.* 2000). Histological findings from the initial biopsy were related to risk of repeat biopsy positive for cancer. Men with both atypical glands suspicious for cancer and HGPIN were at greatest risk of positive repeat biopsy (53%), followed by those with atypical glands suspicious for cancer only (40%), HGPIN only (23%) and no evidence of malignancy (20%).

Predictive factors for positive repeat biopsy (multivariate analyses).

Five papers reported multivariate analysis of predictive factors for positive repeat biopsy (Djavan *et al.* 2000; Eggener *et al.* 2005; Fowler *et al.* 2000; Lopez-Corona *et al.* 2003; Mian *et al.* 2002). One of these studies (Lopez-Corona *et al.* 2003) developed a nomogram for the prediction of repeat biopsy outcome, which has since been validated (Yanke *et al.* 2005). Some papers (Djavan *et al.* 2000; Eggener *et al.* 2005; Fowler *et al.* 2000) only reported statistically significant results from multivariate analysis: it was unclear in these studies whether other variables had been entered into the regression but were not significant.

- **Atypical small acinar proliferation (ASAP)** on a prior biopsy was predictive of a positive future biopsy in the two analyses that included it (Lopez-Corona *et al.* 2003; Mian *et al.* 2002).

- **HGPIN** on a prior biopsy was a independent predictor of positive repeat biopsy in 2 studies (Eggener *et al.* 2005; Lopez-Corona *et al.* 2003) but not in 2 other studies (Fowler *et al.* 2000; Mian *et al.* 2002)
- **Age** was not independently associated with increased risk of positive repeat biopsy in three studies (Fowler *et al.* 2000; Lopez-Corona *et al.* 2003; Roobol et al. 2006) (although age is included in the nomogram of Lopez-Corona). Fowler et al (Fowler *et al.* 2000) found age to be a significant independent predictor of repeat biopsy result.
- **PSAV** was a significant independent predictor of biopsy outcome in (Eggener *et al.* 2005; Lopez-Corona *et al.* 2003) but not in (Fowler *et al.* 2000; Mian *et al.* 2002).
- **PSA-TZD** was a significant independent predictor of biopsy outcome in the Djavan study (Djavan *et al.* 2000).
- **PSAD** was a significant independent predictor of biopsy outcome in the Fowler study (Fowler *et al.* 2000) but not in (Eggener *et al.* 2005).
- **F/T-PSA ratio** was a significant independent predictor of biopsy outcome in (Djavan *et al.* 2000; Fowler *et al.* 2000) but not in (Mian *et al.* 2002).
- **Abnormal DRE** was independently associated with biopsy outcome in (Eggener *et al.* 2005; Roobol et al. 2006) but not in (Lopez-Corona *et al.* 2003; Mian *et al.* 2002)

Morbidity of biopsy

The CRD 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. One study (Paul *et al.* 2004) mailed questionnaires to men after prostate biopsy, 89.3% of respondents said they would be willing to have a repeat biopsy if advised.

Figure 3.2.1

ROC curve for prediction of positive re-biopsy after negative intial biopsy using different cut-off values of PSAD and PSA-TZD
Circle area is proportional to the number in each study (4 studies in total).

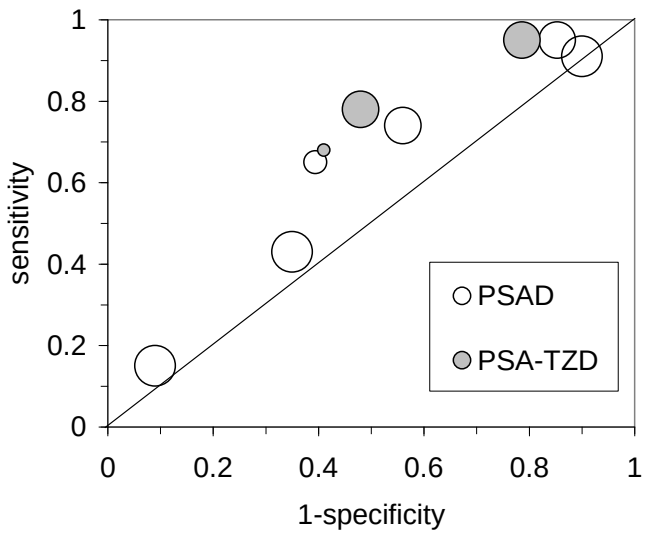


Figure 3.2.2

ROC curve for prediction of positive re-biopsy after negative intial biopsy using different PSAV cut-off values
Circle area is proportional to the number in each study (4 studies in total).

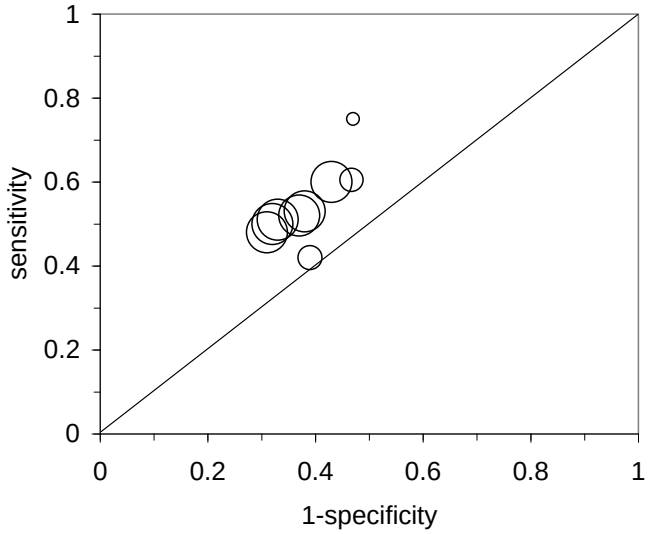


Figure 3.2.3

ROC curve for prediction of positive re-biopsy after negative intial biopsy using different cut-off values of F/T-PSA ratio.
Circle area is proportional to the number in each study (6 studies in total).

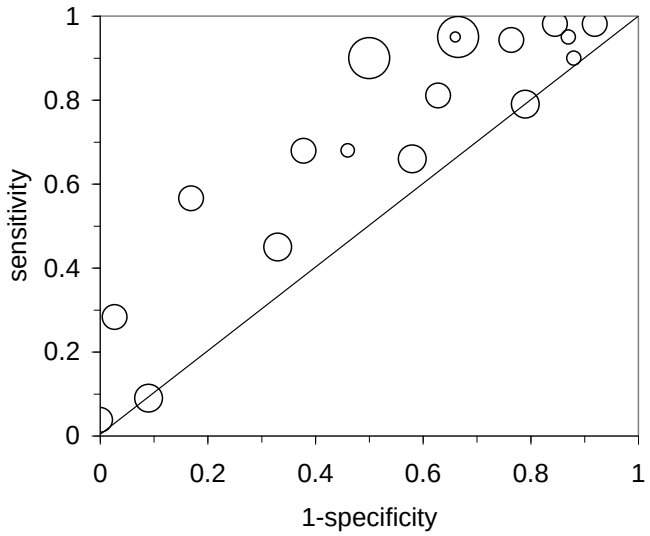
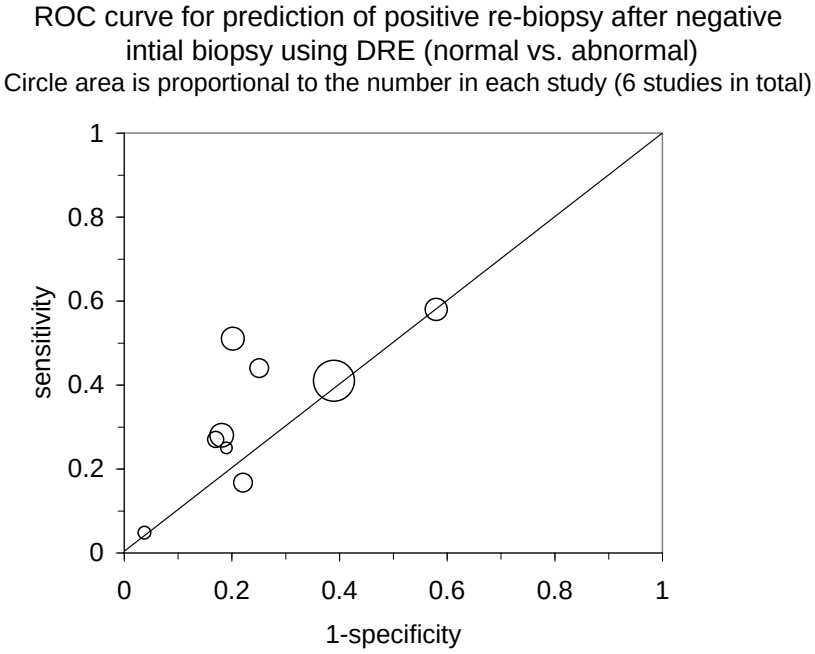


Figure 3.2.4



3.2.1 The relationship between biopsy sensitivity and repeat biopsy sessions

Increased sensitivity is one reason for repeating prostate biopsy in men with symptoms or signs of prostate cancer, but a negative initial biopsy session.

It is possible to estimate the number of repeat biopsy sessions required to achieve a given cancer detection rate (equation 1, below).

The method requires the following assumptions:

- the sensitivity of the prostate biopsy is the same for each session and for all men
- All men with negative or indeterminate biopsies are re-biopsied. Men with positive biopsies are not re-biopsied
- The true disease state for each man (prostate cancer or not) is fixed, before the first biopsy session.
- only tumours potentially detectable by biopsy are considered prostate cancer

$$D_n = 1 - (1-S)^n \qquad \textit{(Equation 1)}$$

Where:

- n is the biopsy session number (1 is the initial biopsy, 2 is the first repeat and so on)
- D_n is the cumulative proportion of cancers detected at biopsy n. This is the probability that a cancer present before the initial biopsy, will have been detected by biopsy session n.
- S is the sensitivity of the biopsy (a fixed value between 0 and 1)

The number needed to biopsy (NNB, the number of biopsy sessions per case of prostate cancer detected) can also be calculated (equation 2).

$$NNB = 1 + \frac{n - Pn + \sum_{i=1}^{i=n} P(1 - S)^{i}}{P - P(1 - S)^{n}} \qquad \textit{(Equation 2)}$$

Where:

- *P* is the prevalence of prostate cancer in men referred for prostate biopsy (a fixed value between 0 and 1). The other variables are already defined above.

Results

Figure 3.2.1.1 below shows the calculated effect of sensitivity on the cumulative proportion of prostate cancers detected. When the biopsy is more sensitive, fewer repeat biopsies are required to achieve the arbitrary detection rate of 99.9%.

If the required detection rate is 99.9% and the sensitivity of the biopsy is 90%, in a given patient, repeated biopsy can stop after 3 negative biopsy sessions. If the sensitivity is 60%, however, 8 negative biopsy sessions will be required before stopping. Table 3.2.1.1 shows the number needed to biopsy (NNB) per case of cancer detected, depending on cancer prevalence and biopsy sensitivity.

Figure 3.2.1.1 Cumulative proportion of cancer detected, for different levels of biopsy sensitivity

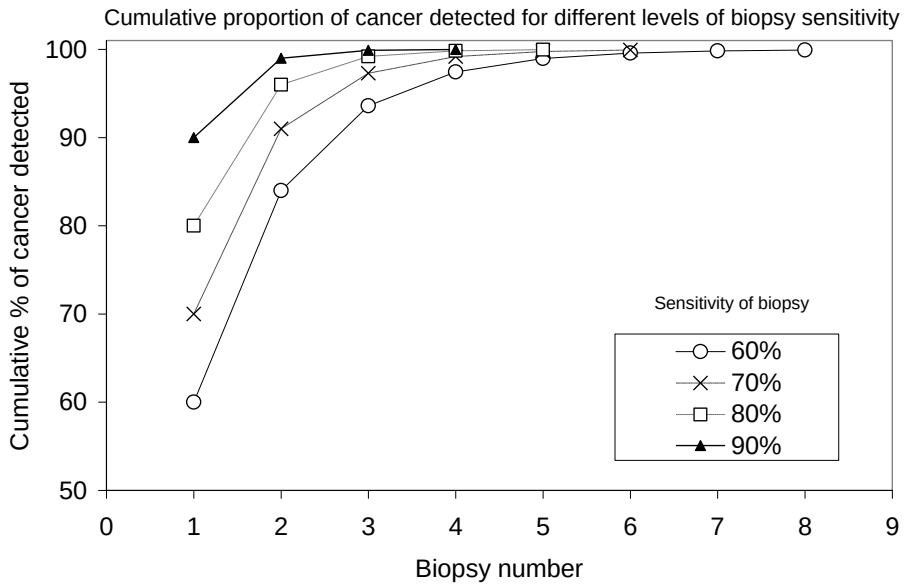
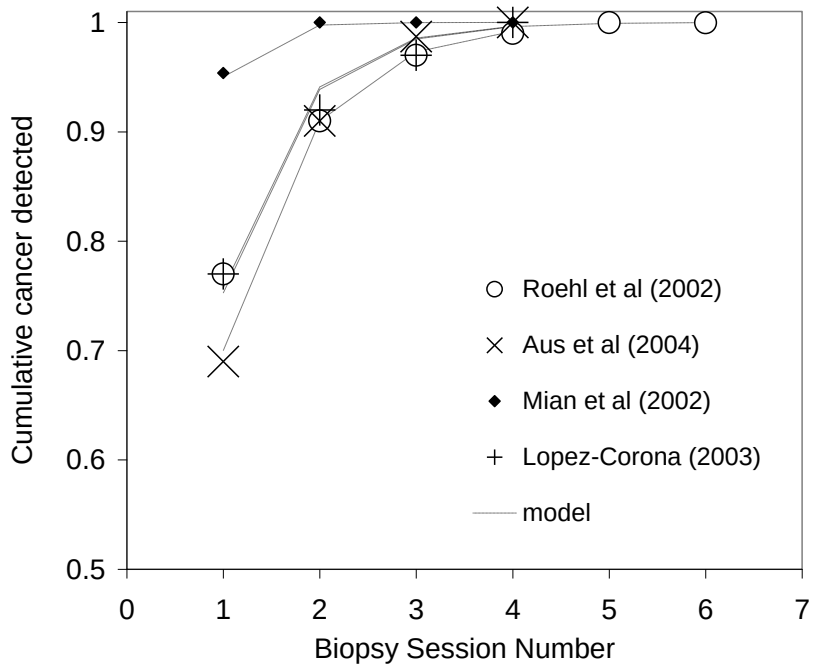


Table 3.2.1.1 Number needed to biopsy (NNB) for each prostate cancer detected, for different values of biopsy sensitivity and prostate cancer prevalence (10%, 30% and 50%).

Sensitivity (%)	Biopsy no.	% PCa detected	NNB (prev. 10%)	NNB (prev. 30%)	NNB (prev. 50%)
90	1	90	11.11	3.7	2.22
	2	99	19.29	5.82	3.13
	3	99.9	28.14	8.12	4.11
80	1	80	12.5	4.17	2.5
	2	96	20	6.11	3.33
	3	99.2	28.47	8.31	4.27
	4	99.84	37.31	10.6	5.26
	5	99.97	46.26	12.92	6.25
70	1	70	14.29	4.76	2.86
	2	91	21.21	6.56	3.63
	3	97.3	29.18	8.62	4.51
	4	99.19	37.72	10.84	5.46
	5	99.76	46.54	13.12	6.44
	6	99.93	55.47	15.44	7.43
60	1	60	16.67	5.56	3.33
	2	84	23.1	7.22	4.05
	3	93.6	30.51	9.15	4.87
	4	97.44	38.61	11.25	5.77
	5	98.98	47.13	13.45	6.72
	6	99.59	55.89	15.72	7.69
	7	99.84	64.77	18.03	8.68
	8	99.93	73.71	20.35	9.67

Roehl and co-workers (Roehl *et al.* 2002) reported a large case series in which a proportion of men with negative quadrant or sextant biopsy underwent repeated biopsy sessions, up to 10 times in some cases. Aus and co-workers (Aus *et al.* 2004) reported a similar series in which there were up to 4 repeat sets of sextant biopsies in a proportion of patients. In the series of Lopez-Corona (Lopez-Corona *et al.* 2003) the initial biopsy was usually sextant biopsy and repeat biopsies usually octant. The series reported by Mian (Mian *et al.* 2002) used an extended (10 or 11 core) template for all biopsies. The model described by equation 1 was fitted in turn to the data from each of these studies using nonlinear regression (SPSS statistics program; see figure 3.2.1.2).

Figure 3.2.1.2 Equation 1 fitted to repeat biopsy data from four series.



The model estimates of sextant biopsy sensitivity are 75% for the Roehl et al (2002) and Lopez-Corona (2003) data and 70% using the Aus et al (2004) data. The estimate of the sensitivity of the extended template used by Mian et al (2002) data is 95%.

The increased sensitivity of the extended template is predicted by the authors of the CRD systematic review of prostate biopsy techniques (Eichler *et al.* 2006) who estimated the cancer yield of this type of 10 core biopsy is 1.38 times that of sextant biopsy.

Validity of the assumptions

- Not all men with negative biopsies will have repeat biopsy (for example, if PSA measures return to normal levels). Men may decline the offer of repeat biopsy.
- Men with undetectable tumours could develop detectable cancer between biopsy sessions, especially when the interval between sessions is long. This would invalidate the assumption about fixed disease state.
- The assumption of fixed sensitivity only holds if the biopsy scheme is same on repeated biopsies. Repeat biopsy schemes using more cores should be more sensitive (Eichler *et al.* 2006). Sensitivity is also likely to depend on tumour characteristics, such as location, grade and volume, and patient characteristics like prostate volume.

Evidence Tables

(Roehl *et al.* 2002)
Design: Prospective case series (diagnosis, screening), evidence level: 3 Country: United States, setting: Secondary care **Inclusion criteria** Men participating in a screening study for prostate cancer. All had 1 or more prostate biopsy, PSA measurement and DRE at a single institution between 1991 and 2000. Age in general 50 years or older, but 40 years or older for high risk cases. **Exclusion criteria** - **Population** number of patients = 2526. **Interventions** TRUS guided prostate biopsy was advised if DRE was suspicious or if serum PSA was raised. The threshold PSA value was 4.0 ng/ml between 1991 and 1995 and 2.5 ng/ml between 1995 and 2000. In the period 1991 to 1995, quadrant TRUS guided biopsies were used, with additional lesion directed biopsies in many cases. From 1995 to 2000, sextant TRUS guided biopsies were the minimum standard. Men whose initial biopsies were negative were advised to return 6 months later for a repeat screening. Not all patients with negative biopsy were re-biopsied and some patients waived an advised re-biopsy session. **Outcomes** Biopsy rates, cancer detection rates. **Results** 962 cases of prostate cancer were detected in the group of 2526 men. All were clinically localised. The maximum number of biopsy sessions for any patient was 10. The cumulative cancer detection rate was 77%, 91%, 97% and 99% for biopsy sessions 1, 2, 3 and 4 respectively. If a fixed sensitivity is assumed, these figures correspond to a sensitivity of approximately 75% for a single biopsy session. 621/962 men diagnosed with prostate cancer had radical prostatectomy. There was a trend for a greater proportion of pathologically localised cancer on repeat biopsies than on the initial biopsy (78% vs. 69%; p =0.05)). The proportion of patients who declined repeat biopsy when it was recommended was 32%, 36%, 40% and 41% for biopsy sessions 2, 3, 4 and 5 respectively.

1 Retrospective cohort study

(Eggener *et al.* 2005)
Design: Retrospective cohort study (diagnosis, screening), evidence level: 3 Country: United States, setting: Community **Inclusion criteria** Men enrolled in a population based PCa screening study, with an initially negative biopsy and serum PSA level between 2.6 and 4.0 ng/ml. Age 40 years or older. Men were enrolled between 1991 and 2001. Criteria for biopsy were PSA greater than 4 ng/ml (1991 to 1996) or greater than 2.5 ng/ml (1995 to 2001) or abnormal DRE. **Population** –n=1202 **Interventions** Initial and repeat biopsies: quadrant (1991 to 1995) and sextant (1995 to 2001), plus lesion directed cores. Interval between biopsies: at least 6 months. DRE: the result at the initial biopsy was used in the analysis. PSAV: calculated using the PSA at the initial negative biopsy and the following PSA measurement. PSAD: measured at initial biopsy. F/T-PSA RATIO: measured at initial biopsy (from 1995 onwards) **Outcomes** The prognostic value of DRE, PSAV, PSAD and F/T-PSA RATIO for positive repeat biopsy. Multivariate analysis was also carried out using these variables and HGPIN on initial biopsy and family history. **Follow up** Men with negative initial biopsy were asked to return for follow up PSA screening at 6 to 12 monthly intervals. 191/1202 (16%) men with negative initial biopsy were lost to follow up. Men not diagnosed with prostate cancer were followed-up for a median of 72 months. **Results** Cancer yield on initial biopsy: 440/24893 Cancer yield on repeat biopsies: 136/1202 (1202 men had at least one repeat biopsy, 376/1202 had further repeat biopsies). Prognostic factors for positive repeat biopsy: PSAD (>0.05 ng/ml/cc): SN=0.90 SP=0.10 PSAD (>0.10 ng/ml/cc): SN=0.43 SP=0.35 PSAD (>0.15 ng/ml/cc): SN=0.15 SP=0.91 PSAV (>0.00 ng/ml/yr): SN=0.60 SP=0.57 PSAV (>0.10 ng/ml/yr): SN=0.53 SP=0.62 PSAV (>0.15 ng/ml/yr): SN=0.52 SP=0.63 PSAV (>0.20 ng/ml/yr): SN=0.51 SP=0.67

PSAV (>0.25 ng/ml/yr): SN=0.50 SP=0.68

PSAV (>0.30 ng/ml/yr): SN=0.48 SP=0.69

F/T-PSA RATIO (<10%): SN=0.09 SP=0.91

F/T-PSA RATIO (<15%): SN=0.45 SP=0.67

F/T-PSA RATIO (<20%): SN=0.66 SP=0.42

F/T-PSA RATIO (<25%): SN=0.79 SP=0.21

ABNORMAL DRE: SN=0.41 SP=0.61

Multivariate analysis identified the following independent prognostic factors (in order of importance): HGPIN on initial biopsy, initial total PSA of more than 3.6 ng/ml, abnormal DRE, family history and PSAV.

1

(Berenguer *et al.* 2003)

Design: Prospective case series (diagnosis, screening), evidence level: 3

Country: Spain, setting: Community

Inclusion criteria Men aged 45 to 70 years with life expectancy of more than 10 years were recruited into a randomised study of prostate cancer screening between 1996 and 2002.

Exclusion criteria Anticoagulant therapy, severe disease, prostate surgery, prior prostate cancer detection and others not stated.

Population number of patients = 4278.

Interventions Men were randomised to one of two arms: screening, with an indication for transrectal ultrasonography (TRUS) and sextant prostate biopsy when the serum prostate-specific antigen (PSA) level was >4 ng/mL (1996 to 1998) and from 1998 to 2002 when the PSA was >2.9 ng/mL; or a control group (no diagnostic tests).

Outcomes Cancer detection rate.

Follow up In the screening arm, men who did not meet the criteria for biopsy were asked to attend a second screening round 4 years later. Men with negative biopsies were asked to attend yearly repeat screening until the second round. 17% of men in whom biopsy was indicated refused biopsy.

Results 2416 men entered the screening arm. 201 met the criteria for biopsy, and 57 cancers were eventually detected in these 201 patients.

40 cancers were detected in the initial 166 biopsy sessions. A further 17 cancers were detected in 130 repeat biopsy sessions. The NNB per case of cancer was therefore 5.19. It is not clear how many repeat biopsies individual patients had, or the compliance with repeat biopsy. Results from the second screening round (4 years after the initial screening) are immature.

2

(Aus *et al.* 2004)
Design: Prospective case series (prognosis), evidence level: 3 Country: Sweden, setting: Community **Inclusion criteria** Men taking part in a randomised trial of prostate cancer screening. Men with total PSA more than 3 ng/ml had biopsy. Age 50 to 65 years. **Exclusion criteria** Existing prostate cancer. **Population** number of patients = 1349. **Interventions** Initial and repeat biopsies: sextant Total PSA, DRE and TRUS were carried out a 6 monthly intervals in men with negative biopsy but persistently elevated PSA. **Outcomes** Cancer detection rate on repeat biopsy. **Follow up** Screening tests were done at 6 monthly intervals. **Results** Cancer yield at first biopsy: 324/1304 (24.8%) Cancer yield at second biopsy: 107/508 (21.1%) Cancer yield at third biopsy: 32/241 (13.3%) Cancer yield at fourth biopsy: 6/76 (8.6%)

(Djavan *et al.* 2000)
Design: Prospective case series (diagnosis, screening), evidence level: 3 Country: Austria, setting: Multicentre **Inclusion criteria** Men referred for prostate biopsy after LUTS or prostate cancer screening between 1997 and 1999. Serum PSA level between 4 and 10 ng/ml. **Exclusion criteria** History of: prostate cancer, prostatitis, prior biopsy, PIN. Current urinary tract infection or indwelling catheter. Patients who refused repeat biopsy. **Population** number of patients = 820. **Interventions** Initial biopsy: sextant + 2 TZ biopsies Repeat biopsies: sextant + 2 TZ biopsies Time between biopsies: 6 weeks PSA-TZD: measured at initial biopsy PSAD: measured at initial biopsy F/T-PSA ratio: measured at initial biopsy **Outcomes** PSA-TZD, PSAD and F/T-PSA as predictive factors for positive repeat biopsy. **Results** Cancer yield on initial biopsy: 231/1051 (22%) Cancer yield on repeat biopsy: 83/820 (10%) Predictive factors for positive repeat biopsy: PSA-TZD (>0.26 ng/ml/cc): sensitivity = 0.78, specificity = 0.52. PSA-TZD (>0.19 ng/ml/cc): sensitivity = 0.95, specificity = 0.21. PSAD (>0.13 ng/ml/cc): sensitivity = 0.74, specificity = 0.44. PSAD (>0.09 ng/ml/cc): sensitivity = 0.95, specificity = 0.15. F/T-PSA RATIO (<30%): sensitivity = 0.90, specificity = 0.50. F/T-PSA RATIO (<38%): sensitivity = 0.95, specificity = 0.34. In a multivariate analysis only F/T-PSA and PSA-TZD were significant predictors of positive repeat biopsy (p<=0.001, standard errors not reported).

(Paul *et al.* 2004)
Design: Prospective case series (diagnosis, screening), evidence level: 3 Country: Germany **Inclusion criteria** Men scheduled for prostate biopsy between May 2000 and April 2001 at a single institution. **Population** number of patients = 405. **Interventions** Men undergoing their first biopsy were randomised to either a 6 or 10 core biopsy. Additional, lesion-directed, biopsy cores were permitted. Men undergoing repeat biopsy had 6 core biopsy with an additional 2 cores from the ventral transition zone, plus lesion directed cores when appropriate. **Outcomes** Morbidity and pain related to the biopsy. Patient acceptance of repeat biopsy. **Follow up** The outcomes were assessed using a self-administered questionnaire 1 week and 1 month after prostate biopsy. 89.9% of patients returned at least one of the two questionnaires. **Results** Morbidity and pain results of this study are reported in CRD report 29, and are not included in this appraisal. 89.3% of patients who responded stated that they would be willing to have a repeat biopsy if advised. 10.7% would not repeat biopsy if advised.

(Roobol *et al.* 2004)
Design: Prospective case series (diagnosis, screening), evidence level: 3 Country: Europe, setting: Multicentre **Inclusion criteria** Men enrolled in the European Randomised Study of Screening for Prostate Cancer (ERSPC), who underwent initial and repeat biopsies. Age 54 to 74. **Population** number of patients = 217, age range 54 to 74 years. **Interventions** Initial biopsy: sextant Repeat biopsy: sextant DRE: performed at initial and repeat visits. **Outcomes** Abnormal DRE as a prognostic factor for positive repeat biopsy. **Results** Cancer yield at initial biopsy: 263/728 Cancer yield at repeat biopsy: 18/217 Prognostic factors for positive repeat biopsy

Abnormal DRE (at initial biopsy): sensitivity= 0.17, specificity=0.78 Abnormal DRE (at repeat biopsy): sensitivity= 0.44, specificity=0.75 **General comments** Mean values of PSAD, PSAV are reported for cancer and non-cancer groups, are not analysed as predictive factors for positive repeat biopsy.

Retrospective case series

(Fowler *et al.* 2000)
Design: Retrospective case series (), evidence level: 3 Country: United States **Inclusion criteria** Men who had an initial negative and repeat prostate biopsy, after abnormal DRE or PSA > 4 ng/ml. Men were biopsied between 1992 and 1999 at a single institution. Criteria for repeat biopsy were raised PSA level or abnormal DRE. **Exclusion criteria** - **Population** number of patients = 298. **Interventions** Initial and repeat biopsies: sextant (1992 to 1995) and sextant + 2 TZ cores (1995 to 1997) and from 1997 to 1999 5 region technique. Interval between biopsies: median 16 months1` DRE: unclear whether the original or repeat examination was used. F/T-PSA RATIO: determined at the time of repeat biopsy. **Outcomes** DRE and F/T-PSA ratio as predictors of positive repeat biopsy. Logistic regression was performed using other variables but not reported fully. **Results** Cancer yield at initial biopsy: 587/1740 Cancer yield at repeat biopsy: 80/298 Prognostic factors for positive repeat biopsy ABNORMAL DRE: SN=0.58 SP=0.42 F/T-PSA RATIO (<40%): SN= 0.98 SP=0.08 F/T-PSA RATIO (<35%): SN= 0.98 SP=0.16 F/T-PSA RATIO (<30%): SN= 0.94 SP=0.24 F/T-PSA RATIO (<25%): SN= 0.81 SP=0.37 F/T-PSA RATIO (<20%): SN= 0.68 SP=0.62 F/T-PSA RATIO (<15%): SN= 0.57 SP=0.83

F/T-PSA RATIO (<10%): SN= 0.28 SP=0.97 F/T-PSA RATIO (<5%): SN= 0.04 SP=1.00 Significant independent prognostic factors on logistic regression were: age and PSAD. In patients with F/T-PSA RATIO measurements F/T-PSA RATIO was a significant predictor of positive repeat biopsy. HGPIN was not a significant predictor of positive repeat biopsy in this series.

1

(Keetch *et al.* 1996)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: United States **Inclusion criteria** Men screened for PCa using PSA test, whose initial biopsy was negative but who had persistently raised serum PSA (>4ng/ml), abnormal DRE or TRUS. **Exclusion criteria** Men with atypia or HGPIN on initial biopsy. **Population** number of patients = 327. **Interventions** Initial biopsy method: 4 to 6 cores in most cases, no TZ biopsies. Repeat biopsy method: same as initial biopsy Time between initial and repeat biopsy: minimum 6 months PSAD measured: at initial biopsy PSAV measured: using initial and most recent biopsies DRE: used most recent examination **Outcomes** The sensitivity and specificity of abnormal DRE, PSAD, and PSAV for the prediction of positive re-biopsy. **Follow up** Men negative initial biopsy had PSA test at 6 month intervals, and were advised to have re-biopsy if it was indicated. **Results** Cancer yield at initial biopsy: not reported Cancer yield at repeat biopsies: 81/327 (25%). Prognostic factors for positive repeat biopsy: PSAD: sensitivity=0.65, specificity=0.61 PSAV: sensitivity=0.61, specificity=0.53 Abnormal DRE: sensitivity=0.51, specificity=0.80

2

3

1

(Mian *et al.* 2002)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: United States **Inclusion criteria** Men who had a repeat extended template prostate biopsy, following an initial negative extended template prostate biopsy at a single institution between 1997 and 2001. **Exclusion criteria** - **Population** number of patients = 89, age range 44 to 74 years, median age = 61 years. **Interventions** Initial and repeat biopsies: extended template (10 or 11 cores incorporating the anterior horn of the PZ) Interval between biopsies: median 4 months (range 1 to 36 months). **Outcomes** Patient age, interval between biopsies, total PSA, F/T-PSA ratio, TRUS findings, DRE findings, prostate volume, HGPIN on initial biopsy, and atypical suspicious glands on initial biopsy were entered as variables in multivariate regression, to identify independent predictors of positive repeat biopsy. **Results** Cancer yield at initial biopsy: 310/939 (33%) Cancer yield at first repeat biopsy: 15/89 (17%) Cancer yield at second repeat biopsy: 0/8 (0%) Cancer yield at third repeat biopsy: 0/1 (0%) The only statistically significant independent predictor of positive biopsy (from multivariate regression) was atypical glands suspicious for cancer on initial biopsy ($p<0.001$). HGPIN on initial biopsy approached significance ($p=0.057$). - **General comments** Small series. Too large a number of predictive variables analysed for the small event rate.

2

(O'Dowd *et al.* 2000)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: United States **Inclusion criteria** Cases were submitted by private practice urologists throughout the USA between 1994 and 1998, and processed by a single laboratory: UroCor Labs (Oklahoma City, OH, USA). Patients with repeat biopsy within 1 year of the first were chosen for analysis.

Population number of patients = 132426.

Interventions Prostate biopsy, repeated within a year of initial biopsy. A subset of patients (n=855) had tPSA, fPSA and f/t PSA ratio measurements between the initial and repeat biopsies. In most cases, the number of cores taken for each biopsy set was between 6 and 8, although 19% of patients only had biopsy sets with 5 cores or less.

Outcomes Pathology diagnosis on initial and repeat biopsy. Possible pathology diagnoses were: positive (prostate cancer), high-grade prostatic intraepithelial neoplasia (HGPIN), atypical glands suspicious for cancer (suspicious), suspicious with HGPIN (susp-HGPIN) and no evidence of malignancy (NEM).

Cancer detection rate on repeat biopsy was analysed by initial diagnosis.

Results The time between the initial and repeat biopsy did not appear to be associated with cancer detection rate (within the one year range analysed).

COMPARISON IN MEN UNDERGOING PROSTATE BIOPSY	NEM	HGPIN	SUSPICIOUS LESION	SUSPICIOUS/HGPIN	CANCER	OVERALL RESULT
Initial biopsy diagnosis	73294 (55.3%), 3544 (4.8%) had repeat biopsy	4902 (3.7%), 1306 (26.6%) had repeat biopsy	3269 (2.5%), 1321 (40.4%) had repeat biopsy	440 (0.3%), 209 (47.5%) had repeat biopsy	50521 (38.2%), none had repeat biopsy	Total n=132426, repeat biopsy rate depended on initial diagnosis
Repeat biopsy diagnosis	4231 (66.3%)	322 (5.0%)	170 (2.7%)	20 (0.3%)	1637 (25.7%)	Total n=6380
Repeat biopsy cancer detection rate, by initial diagnosis	702 (19.8%)	295 (22.6%)	529 (40%)	111 (53.1%)	NA	Total n=1637. Patients with suspicious lesions (+-HGPIN) on initial biopsy were at greatest risk of cancer

1

(Satoh *et al.* 2005)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: Japan **Inclusion criteria** Men who had transperineal ultrasound guided prostate biopsy. All had undergone at least one negative set of TRUS guided biopsies. The indications for the transperineal biopsy were elevated PSA (>2.1 ng/ml), abnormal DRE, HGPIN on prior biopsy and atypia on prior biopsy. **Exclusion criteria** - **Population** age range 37 to 85 years, median age = 67 years. **Interventions** All men underwent systemic ultrasound-guided biopsy using the transperineal template technique, with spinal anaesthesia. Four biopsies were obtained anterior to posterior from each of four coronal planes in the mid-region, and three biopsies were obtained anterior to posterior from each of two coronal planes in the apical region (22 cores). PSA levels were also measured. All men had at least one prior set of negative TRUS guided biopsies. The median number of prior biopsy sets was 1 (range 1 to 5). The median number of cores in the prior biopsy sets was 6 (range 4 to 12). **Outcomes** Cancer detection rate. Adverse events. **Results** Prostate cancer was detected in 29/70 men. PSA levels were significantly higher in those with prostate cancer than in those with negative transperineal biopsy (group means 11.4 vs. 7.6 ng/ml respectively, p=0.0012). In men with one previous TRUS guided biopsy set the cancer detection rate was 13/70 (18.6%), compared to 16/58 (26%) in men with two prior negative sets of TRUS biopsies. The difference was not statistically significant. The adverse event rate was 3.9% with 5/128 patients having an adverse event. One patient had prostatitis requiring hospitalisation, two had urinary retention and two had difficult urination after the biopsy.

2

(Singh *et al.* 2004)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: United States **Inclusion criteria** Men who had repeat prostate biopsy, after an initial negative biopsy session. Criteria for repeat biopsy included F/T-PSA ratio of 15% or less with total PSA persistently greater than 3 ng/ml and/or PSAV of 0.75 ng/ml/year. **Exclusion criteria** -

Population -

Interventions Initial biopsy: S12C template

Repeat biopsy: minimum S12C template

Interval between biopsies: at least 3 months (median 4 months)

F/T-PSA RATIO: measured at repeat biopsy

PSA-TZD: measured at initial biopsy

PSAV: calculated using at least 3 serial PSA measurements, over a median time of 3 years.

DRE: result at initial biopsy used for analysis

Outcomes F/T-PSA ratio, PSAV, PSA-TZD, and abnormal DRE as predictive factors for positive repeat biopsy.

Follow up Patients were underwent DRE and PSA evaluation within 3 to 6 months of the initial negative biopsy and 6 monthly thereafter. Those meeting the criteria were re-biopsied.

Results Cancer yield at initial biopsy: 312/814 (44%)

Cancer yield at repeat biopsy: 21/99 (21%)

Predictive factors for positive repeat biopsy:

F/T-PSA ratio (<12%) : sensitivity = 0.68, specificity = 0.54

PSAV (>0.93 ng/ml/yr) : sensitivity = 0.75, specificity = 0.53

PSA-TZD (>0.93 ng/ml/cc) : sensitivity = 0.68, specificity = 0.59

DRE (abnormal): sensitivity = 0.05, specificity = 0.96

General comments Patients restricted to relatively high risk cases (F/T-PSA < 15%). Unclear what the criteria for the initial biopsy were, and how patients were referred in the first place.

1

(Stewart *et al.* 2001)

Design: Retrospective case series (diagnosis, screening), evidence level: 3

Country: United States

Inclusion criteria Men who had saturation biopsy of the prostate between 1996 and 1999. Men had at least one previous negative sextant prostate biopsy session (mean 1.8, range 1 to 7), and persistent indication for repeat biopsy. Indications for repeat biopsy were: persistent PSA > 4ng/ml, abnormal DRE, atypia on previous biopsy and HGPIN on previous biopsy.

Exclusion criteria -

Population number of patients = 224, age range 44 to 81 years, mean age = 64 years.

Interventions All men had saturation ultrasound guided transrectal prostate needle biopsy

under general anaesthesia in an outpatient surgical setting. A mean of 23 cores (range 14 to 45) were obtained at each session, with larger prostates requiring more cores.

Outcomes Cancer detection rate. Adverse event rate.

Results 27/224 patients experienced an adverse event. The most serious was symptomatic bacteraemia in 1 case. Hematuria requiring hospitalisation occurred in 12/224 patients and 10/224 men had urinary retention.

There was no trend of decreasing yield of saturation biopsy with an increasing number of prior sextant biopsies (p=0.75), suggesting that the sextant biopsies were insensitive to the type of cancers detected by the saturation biopsy.

Univariate analysis of initial PSA, PSA at saturation biopsy, age, number of cores, patient age and number of previous negative biopsies showed only patient age to be significantly associated with prostate cancer on saturation biopsy (p=0.015).

COMPARISON IN MEN UNDERGOING PROSTATE SATURATION BIOPSY	BENIGN TISSUE	PROSTATE CANCER	HGPIN OR ATYPIA	INFLAMMATION	OVERALL RESULT
Pathological findings	104/224 (47%)	77/224 (34%)	19/224 (8%)	24/224 (11%)	

General comments Multivariate analysis of prognostic factors for PCa on saturation biopsy would have been helpful.

1

(Rabets *et al.* 2004)

Design: Retrospective case series (diagnosis, screening), evidence level: 3

Country: United States

Inclusion criteria Men who were believed to be at risk for prostate cancer after at least one set of negative prostate biopsies 2002 and 2003. Risk factors included atypia or PIN on biopsy and PSA persistently greater than 2.5 ng/ml.

Exclusion criteria -

Population number of patients = 116.

Interventions All men had saturation prostate biopsy with local anaesthesia during which between 20 and 24 cores were obtained.

Outcomes Cancer detection rate. Adverse events.

Results The cancer detection rate was 34 from 116 saturation biopsies (29%). The detection rate was 23/70 (33%), 7/28 (25%), and 4/18 (22%) for patients with 1, 2 and 3 or more prior biopsy sessions.

One patient had palpitations and shortness of breath after the injection of lidocaine. Two

patients reported light-headedness and one had outpatient treatment for rectal bleeding.

1

(Roobol *et al.* 2006)
Design: Prospective cohort study (diagnosis, screening), evidence level: 2+ Country: Netherlands, the, setting: Community **Inclusion criteria** Men included in the ERSPC screening study. **Exclusion criteria** Age > 75 years. Symptoms of prostate cancer before first screening visit. **Population** number of patients = 1091, age range 55 to 75 years. **Interventions** All men were screened for prostate cancer: indication for biopsy was PSA > 3.0 ng/ml. 4 years later screening was repeated in the men without prostate cancer. **Outcomes** Biopsy outcome (positive for prostate cancer or not). **Follow up** 1091 men were initially screened. 9650 men were eligible for a second screening but 3430 (36%) were not screened due to: death, age >75 years, moving away, comorbidity or refusal. **Results** Of 10191 men screened in the first round, 1850 were biopsied and there were 541 cases of prostate cancer. Of the 6220 men screened in the second round, there were 1040 men biopsied with 197 cases of prostate cancer. Logistic regression models were reported for predicting the outcome of first and second round biopsies. Odds ratios (and 95% confidence intervals) for positive 1st biopsy were: PSA > median value OR = 2.3 (95% CI 1.8 to 2.9), DRE & TRUS suspicious OR = 6.0 (95% CI 4.4 to 8.1) prostate volume > median OR = 0.4 (95% CI 0.3 to 0.5) positive family history OR = 1.7 (95% CI 1.2 to 2.4) age > median age OR = 1.2 (95% CI 1.0 to 1.5) Odds ratios (and 95% confidence intervals) for positive 2nd biopsy (after an initial negative one) were: PSA > median value OR = 6.9 (95% CI 1.2 to 39.5), DRE & TRUS suspicious OR = 2.8 (95% CI 1.7 to 4.7) prostate volume > median OR = 0.5 (95% CI 0.3 to 0.7) previous negative biopsy OR = 0.5 (95% CI 0.3 to 0.7) positive family history OR = 1.8 (95% CI 1.0 to 3.2)

2

(Celhay *et al.* 2007)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: France, setting: Tertiary care **Inclusion criteria** Men were selected from the records of two teaching hospitals, if they had a first negative prostate biopsy followed by at least one other prostate biopsy. **Population** number of patients = 191, age range 47 to 81 years, median age = 63 years. **Interventions** All 191 men had at least two sets of biopsies. 58 men had three sets of biopsies and 10 had four sets. All were taken transrectally under TRUS guidance and at least 12 cores were taken in each session. A 'fluctuating PSA level' was defined as a PSA series with at least one PSA value lower than the one immediately preceding it. In all other cases, PSA was considered steady. **Outcomes** Repeat prostate biopsy positive for prostate cancer. **Follow up** The median interval between first and second biopsy was 297 days for men with prostate cancer and 287 for those without cancer. **Results** Prostate cancer was eventually found in 53/191 (38%) men: 39 at the second biopsy set, 12 at the third and 2 at the fourth. The sensitivity and specificity of steady PSA level for positive repeat biopsy were 68% and 55% respectively. The poor sensitivity and specificity suggest fluctuating PSA is unlikely to be a useful predictor of repeat biopsy result.

1

(Park *et al.* 2006)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: Canada (federal state, Commonwealth Realm), setting: Tertiary care **Inclusion criteria** Men with unilateral core involvement on prostate biopsy, who were then treated with radical prostatectomy **Exclusion criteria** Men with neoadjuvant hormone therapy or with more than one set of biopsies. **Population** number of patients = 70. **Interventions** All men had a 10 core TRUS biopsy. All men had radical prostatectomy. Morphometric analysis was conducted on the biopsy-negative hemi-prostates to determine the predictive value of the biopsy protocol with respect to the size, position and clinical significance of the lesion. **Outcomes** Clinically significant prostate cancer in the ipsilateral and contralateral prostate lobes (to the lobe with positive biopsy cores). **Results** Prostate cancer was confirmed in the ipsilateral half of the resected prostate in all 70

cases with unilaterally positive biopsy sets. Prostate cancer was detected in the contralateral half of the prostate in 38/70 (54%) of these cases, while 32/70 cases did not have prostate cancer in the contralateral lobe.

8 cases of significant cancer were seen in the lobe that was negative for prostate cancer on the biopsy. Thus clinically significant cancer was missed in 8/70 (11%) of hemiprostates negative for cancer on biopsy.

General comments The applicability to men with a completely negative first prostate biopsy is unclear.

Health Economic Summary

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.

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3.3 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?

Health Economics Short Summary

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 treatment 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.

Health Economic Evidence Summary

Overview

Jager et al attempted to determine the appropriate use of magnetic resonance imaging (MRI) for preoperative staging of prostate cancer, with a view to radical therapy.

The overall modelling approach (a decision tree) was considered to appropriate, and the study is well written. However, as the authors acknowledge, the main limitation with the study is the relatively poor quality of the clinical evidence used to populate the model. Particuarly as no studies assessing the theraputic efficacy of MRI in this population were identified. The authors concluded that the results of the modelling were inconclusive in terms of demonstrating cost-effectiveness, but the probability MRI was cost-effective increased significantly as the probability of prior extracapsular disease increased.

Comparison(s)

MRI with a view to choosing appropriate people for radical surgery was compared to radical surgery based on clinical staging alone; people with Gleason scores of between 5-7

Population Sample

A hypothetical cohort of men (with a mean age of 65 years) with prostate cancer for whom radical surgery is being considered.

Costs

Only US health care costs were included. They were based on a literature review, and included the costs of MR imaging, surgery, treatment for complications and palliative treatment. The price year was not stated; US$. Costs over 1-year were not discounted.

Clinical Effectiveness

The clinical effectiveness of MRI and surgery alone were based on a review of the literature. Sensitivity / specificity parameter pairs were derived from a receiver operating curve from a single reference, 57% / 96% being the 'most preferred option'. 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. Health outcomes were expressed in terms of life-years gained and quality-adjusted life-years (QALYs).

Results

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. The total costs were 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

A number of one- and two-way sensitivity analysis were performed, including on the sensitivity and specificity of MRI, the surgical costs and probability of surgical mortality. The MRI strategy dominated the no MRI stratergy when the prior probability of extracapsular disease was at least 39% (in terms of costs and QALYs) and 50% when considering (costs and life-years gained).

Reviewer Comments

The authors concluded that the cost-effectiveness of MRI was yet to be established in this patient group, but the probability MRI was cost-effective increased significantly as the probability of prior extracapsular disease increased. The authors conclusions appear to be reasonable given the quality of evidence used to populate the model; the main limitation with the analysis is that no randomised evidence was found in which MRI versus no MRI had been compared. Thus estimates of clinical effect were not based on randomised studies.

Health Economic Evidence Table

Question: In men with clinically localised prostate cancer for whom radical treatment is intended, what is the cost-effectiveness of different diagnostic imaging options?

Bibliographic reference	Jager, GJ et al. Prostate Cancer Staging: Should MR Imaging Be Used? – A Decision Analytic Approach. 2000, Radiology 215 (2) p. 445-451
Source of funding	Unclear
Economic study type	Cost-Effectiveness Analysis (CEA, using life-years gained) and Cost-Utility Analysis (CUA)
Population, country & perspective	Clinically localised prostate cancer, US ($), health
Technology	MRI (magnetic resonance imaging), plus clinical staging
Comparison(s)	No MRI, clinical staging alone
Source of effectiveness data	Non-RCT based data with modelling
Cost components included and health care resource utilization (HCRU)	Included: costs of MRI, surgery, treatment for impotence / incontinence and palliative treatment
Results – cost per patient per alternative	MRI: $10,568; No MRI $11,669
Results – effectiveness per patient per alternative	MRI: 12.59 years and 12.53 QALYs No MRI: 12.60 years and 12.52 QALYs
Incremental cost-effectiveness ratio	$110,100 per additional Life-Years Gained No-MRI was less costly and more effective for the CUA
Results-uncertainty	Deterministic one- and two-way sensitivity analysis. Results highly dependent on the prior probability of extracapsular disease
Time horizon, discount rate	? Benefits ?%; Costs ?%
Comments	Reasonable quality analysis. Authors stated that there was insufficient evidence to conclusively determine whether MRI staging

	was appropriate. Only MRI was considered, not any other type of staging technique (other than standard clinical staging). Results highly dependent on the prior probability of extracapsular disease, which suggests that the MRI might be more cost-effective in particular sub-groups

Health Economic Quality Checklist

(Drummond and Jefferson 1996 BMJ 13, 275-283 (August))

Scoring - yes, no, not clear and not appropriate	Study ID	Jager et al. 2000
	Checklist completed by	Alec Miners
Study design	Was a research question stated?	Yes
	Was the economic importance of the research question stated?	Yes
	Was the viewpoint/s of the analysis clearly stated and justified?	Yes
	Was the rational for choosing the alternative programs or interventions to be compared stated?	Yes
	Were the alternatives being compared clearly described? (that is, can you tell who? did what? to whom? where? and how often?)?	Yes
	Was the form of economic evaluation used, clearly stated?	Yes
	Is the choice of the economic evaluation justified in relation to the questions addressed?	Yes
Data collection	Was the source of the effectiveness estimates used clearly stated?	Yes
	Were the details of the of the design and results of the effectiveness study given? (if based on a single study)	Partially
	Were the details of the synthesis or meta-analysis of estimates given? (If based on an overview of a number of effectiveness studies)	N/A
	Was the primary outcome measure/s for the economic evaluation clearly stated?	Yes
	Were the methods to value health states and other benefits stated?	Partially

	Were the details of the subjects from whom valuations were obtained given?	Partially
	Were any productivity changes (if included) reported separately?	N/A
	Was the relevance of any productivity changes to the study questions discussed?	N/A
	Were the quantities of resources reported separately from their unit costs?	Partially
	Were the methods for estimation of quantities and unit costs described?	Partially
	Was the currency and price data recorded?	No price year
	Were the details of currency of price adjustments for inflation or currency conversion given?	Unclear
Modelling	Were the details of any model used given?	Yes
	Was the choice of model and the key parameters on which it was based justified?	Yes mostly
Analysis and interpretation of results	Was the time horizon of costs and benefits stated?	Unclear
	Was the discount rate stated?	Unclear
	Was the choice of discount rate justified?	N/A
	Was an explanations given if costs or benefits were not discounted?	N/A
	Were the details of statistical tests and confidence rates given for stochastic data?	N/A
	Was the approach to sensitivity analysis given?	Yes
	Was the choice of variables for sensitivity analysis justified?	Partially
	Were the ranges over which the variables are varied stated?	Partially
	Were relevant alternatives compared?	Yes
	Was the incremental analysis reported?	Yes
	Were the major outcomes presented in a disaggregated as well as aggregated form?	Yes
	Was the answer to the study question given?	Yes
	Did the conclusions follow from the data reported?	Yes
	Were the conclusions accompanied by the appropriate	Yes

	caveats?	
This and the following have been retained from Appendix G	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (for example, distribution of costs and consequences, or relevant ethical issues)?	Yes partially
	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	No
OVERALL ASSESSMENT OF THE STUDY	How well was the study conducted? *Code ++, + or –*	+
	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes

1

4 Localised prostate cancer

4.10 What is the most effective active surveillance protocol?

Short summary

A systematic review by Martin and co-workers (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 three months and every six months thereafter. Some of the protocols involved routine TRUS guided prostate biopsies. The review did not contain any evidence about the use of MRI or MRS in active surveillance. There was no evidence about whether changing the frequency of these tests influences outcomes.

PICO

POPULATION	INTERVENTION and COMPARISON	OUTCOME
Men whose prostate cancer is being followed by active surveillance	Compare active surveillance methods that differ by: • Frequency of PSA testing • Frequency of MRI • Biopsy	Cancer specific survival Overall survival Rate of radical intervention

(The search strategy developed from this PICO table and used to search the literature for this question is in Appendix C)

Evidence summary

A systematic review by Martin and co-workers (Martin *et al.* 2006) compared protocols for the active surveillance of men with untreated clinically localised (T1–T2) prostate cancer. Five relevant case series with predefined measures of disease progression were included, with 451 patients in total. Only one of the series had more than 100 patients and only one had median follow up of more than five years. Three of the series were prospective (Choo et al. 2002; Mohler et al. 1997; Khan et al. 2003).

Table 4.10.1 Active surveillance protocols for of men with untreated clinically localised prostate cancer (Martin *et al.* 2006)

			Frequency of tests used in active surveillance			
Study	Median follow up (years)	n	PSA	DRE	Biopsy	Other
(Chen *et al.* 2003)	7.3	52	3–6 monthly	3–6 monthly	–	–
(Patel *et al.* 2004b)	3.7	88	3–6 monthly	3–6 monthly	At 6 months or if indicated	–
(Choo *et al.* 2002a)	2.4	206	3–6 monthly	3–6 monthly	At 1.5 to 2 years	Bone scan at 1 year
(Mohler *et al.* 1997)	1.9	27	3–6 monthly	3–6 monthly	–	–
(Khan *et al.* 2003a)	1.9	78	6 monthly	6 monthly	Yearly	–

The only consensus appeared to be the use of PSA tests and DRE in active surveillance, initially at a frequency of every three months and every six months thereafter. Some of the protocols (Patel *et al.* 2004a; Choo *et al.* 2002b; Khan *et al.* 2003b) involved routine TRUS guided prostate biopsies. The review did not contain any evidence about the use of MRI or MRS in active surveillance. There was no evidence about whether changing the frequency of these tests influences outcomes.

Health Economic Summary

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.

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4.14 In men who have been treated with radical radiotherapy for prostate cancer what are the effective interventions for radiation toxicity (specifically damage to the bowel)?

Due to the lack of good evidence for this question, the guideline development group commissioned an expert position paper (see appendix B).

Short Summary

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 radio-protective agents. 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.

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men who have had radiotherapy for prostate cancer	Therapies for radiation toxicity (specifically damage to bowel)	Not specified	• Quality of life • Bowel function

(The search strategy developed from this PICO table and used to search the literature for this question is in Appendix C)

Evidence Summary

Many of the studies were not restricted to prostate cancer but included any patients with any malignancy requiring pelvic EBRT.

Evidence summary

Acute radiation bowel toxicity

- *Radio-protective agents (or prophylactic treatments)*
    - *Aminosalicylates* One trial reported a beneficial effect of sulphalazine (Kiliç et al. 2000). One trial reported a beneficial effect of balsalazide on acute proctitis (Jahraus *et al.* 2005). Other aminosalicylates (5-ASA, olsalazine, and mesalazine) were not effective (Baughan *et al.* 1993; Martenson *et al.* 1996; Resbeut *et al.* 1997; Freund *et al.* 1987; Jahraus *et al.* 2005) and often increased the severity of diarrhoea.

- *Sucralfate* although early trials suggested effectiveness, a meta-analysis of 6 randomised trials did not show a benefit of sucralfate for the prevention of acute diarrhoea after pelvic EBRT (Hovdenak *et al.* 2005), some of the trials noted increased bowel toxicity in the patients treated with sucralfate.
- *Glutamine* A single trial did not demonstrate a beneficial effect of glutamine (Kozelsky *et al.* 2003).
- *Clays.* One trial showed a beneficial effect of the clay smectite on prevention of acute diarrhoea (Hombrink et al. 1995).
- *Prostaglandin analogue (misoprostol)*. One small trial (Khan et al. 2000) showed effectiveness of misoprostol for prevention of acute and chronic radiation proctitis. A second, larger, trial (Hille et al. 2005) did not support this finding and noted increased risk of rectal bleeding in the misoprostol group.
- *Bulking agents*. In one trial (Murphy et al. 2000) treatment with psyllium bulking agent (Metamucil) reduced the incidence and severity of diarrhoea compared to standard care.
- *Nutritional intervention*. A systematic review of nutritional interventions during pelvic RT (McGough *et al.* 2004) concluded that low-fat diet, probiotic supplementation and elemental diet may help to prevent acute gastrointestinal symptoms.
- *Others.* Treatments which were not effective for the prevention of acute bowel toxicity during pelvic radiotherapy, in single randomised trials, included: proteolytic enzymes (Martin et al. 2002) and colestipol (Stryker *et al.* 1983).

- *Opiates*. A placebo controlled trial demonstrated the effectiveness of loperamide for the treatment of acute radiation induced diarrhoea (Sherman et al. 1989).
- *Somatostatin analogues*. A randomised controlled trial demonstrated greater effectiveness of octreotide for the treatment of acute radiation induced diarrhoea (Yavuz et al. 2002) than standard co-phenotrope treatment. Patients treated with octreotide were also able to resume their course of radiotherapy sooner than the co-phenotrope group.
- *Butyrate* A placebo controlled trial demonstrated the effectiveness of butyrate enema for the treatment of acute radiation induced diarrhoea (Vernia et al. 2000)
- *Ibuprofen* did not significantly reduce GI symptoms in patients with acute radiation toxicity (Coleman *et al.* 2002).

Late radiation toxicities

- *Overall findings from Cochrane review* (Denton et al. 2002):
  - Rectal sucralfate showed greater clinical improvement for proctitis than anti-inflammatories (odds ratio (OR) 14.00, CI 1.46 to 134.26; n=1 study), though no difference was seen for endoscopic improvement (OR 2.74, CI 0.64 to 11.76, n=1 study).
  - The addition of Metronidazole to the anti-inflammatory regime also appeared to improve the response rate, as measured by reduction in rectal bleeding, diarrhoea, erythema and ulceration (n=1 study). Similarly rectal hydrocortisone appeared to be more effective than rectal betamethasone for clinical improvement although no difference was seen in endoscopic improvement (n=1 study).
  - Short chain fatty acid enemas did not appear to be effective compared to placebo (n=2 studies).
  - Comparing the heater probe and bipolar electrocautery (n=1 study), there was no discernible difference for severe bleeding after one year,

but the heater probe demonstrated a greater increase in the haematocrit and reduced transfusion requirements.

- *Nutritional intervention*. A systematic review of nutritional intervention following pelvic RT (McGough *et al.* 2004) concluded that there was insufficient evidence to recommend the use of specific nutritional interventions for chronic GI symptoms in this group. The authors suggested that low-fat diets, antioxidant vitamins and probiotic supplementations are possibly beneficial. A small placebo controlled trial (Ehrenpreis et al. 2005) showed a greater improvement in late radiation bowel symptoms in patients treated with vitamin A than in a placebo group.
- *Hyperbaric oxygen therapy (HBOT):* One trial, reported in the review by Bennett and co-workers (Bennett et al. 2005), showed an improved chance of healing after HBOT.

Quality of life

Gami and co-workers (Gami *et al.* 2003) reported that diarrhoea adversely affects quality of life in almost half of patients one year after EBRT for prostate cancer.

Evidence table

Systematic reviews of RCTs

(Bennett *et al.* 2005)

Design: Systematic review of RCTs (therapy), evidence level: 1++

Inclusion criteria The review included randomised controlled trials that compared the effect of a regimen including hyperbaric oxygen therapy (HBOT) with any treatment regimen not including HBOT, in patients with late radiation tissue injury. Patient population included those with any later radiation tissue injury of any tissue.

Exclusion criteria -

Population number of patients = 68.

Interventions One unpublished trial of HBOT for radiation necrosis was identified (other anatomical areas are not included in this appraisal). The treatment group received HBOT: 120 minutes 100% oxygen at 2.0 ATA for 30 to 40 sessions over 6 to 8 weeks. The control group had sham treatment in the compression chamber, but breathing air at 1.5 ATA.

Outcomes Primary outcomes were complete resolution of tissue damage (or necrosis) and improvement in LENT-SOMA scale.

Results From the single trial (Clarke, 2004) there was a significantly improved chance of healing following HBOT for radiation proctitis. The trial was unpublished, however, and a sensitivity analysis for missing data showed that no significant effect of HBOT was possible (in the worst case scenario).

COMPARISON IN PATIENTS WITH PROBLEMATIC RADIATION PROCTITIS	HYPERBARIC OXYGEN THERAPY	PLACEBO	OVERALL RESULT
LENT-SOMA	Mean (SD) improvement at 3 months 4.70 (4.70)	Mean (SD) improvement at 3 months 0.73 (4.10)	In favour of HBOT, WMD 3.97 [95% CI 1.69 to 6.25]
Complete resolution of problem	At 3 months 16/34	At 3 months 6/34	In favour of HBOT, RR = 2.67 [95% CI 1.19 to 5.99]

General comments -

1 Randomized controlled trials

(Kiliç *et al.* 2000)

Design: Randomized controlled trial (therapy), evidence level: 1

Country: Turkey, setting: Tertiary care

Inclusion criteria Patients with histologically confirmed cancer in the pelvis, without evidence of distant metastases, who were due to receive pelvic EBRT. Karnofsky performance status of 70 or more.

Exclusion criteria Non functioning rectum, prior history of pelvic or abdominal radiation, perineum included in the EBRT volume, stool incontinence, stool frequency of more than 6 per day, history of irritable bowel symptom, known salicylate sensitivity, and current or prior use of any 5-ASA drug.

Population number of patients = 87.

Interventions All patients received pelvic EBRT to a dosage of between 46 and 50- GY in 23 to 25 fractions. Tumour boost with brachytherapy or EBRT was used where appropriate. Patients were randomised to either sulphasalazine or placebo groups. Two tablets twice daily of sulphasalazine (500 mg) or placebo were administered orally. Treatment was discontinued if patients experienced greater than 7 stools per day than their pretreatment value.

Outcomes The primary endpoint, diarrhoea, was graded on a scale of 0 to 4 using the NCI criteria. Toxicity was assessed weekly by the treating doctor during the first 5 weeks of EBRT and graded using the LENT-SOMA scale.

Follow up Toxicity was assessed weekly during the first 5 weeks of EBRT. There were no losses to follow up.

Results No complications due to the drug were reported.

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT	AMINOSALICYLATE (SULFASALAZINE)	PLACEBO	OVERALL RESULT
Diarrhoea	Any grade 24/44 (55%), grade 2 or worse 12/44 (27%)	Any grade 37/43 (86%), grade 2 or worse 21/43 (49%)	in favour of sucralfate, p=0.038
LENT-SOMA	Percentage with max. LENT-SOMA score: 0 (20%), 1 (66%), 2 (14%), 3 (0%), 4 (0%)	Percentage with max. LENT-SOMA score: 0 (7%), 1 (14%), 2 (32%), 3 (4%), 4 (0%)	difference not statistically significant, p=0.07

General comments -

2

(Baughan *et al.* 1993)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Patients due to receive radical pelvic EBRT. A variety of treatment volumes and dosages were included, but the randomisation attempted to balance these variables between treatment arms. The majority of patients had bladder or prostate cancer (76%).

Exclusion criteria Renal failure, ulcerative colitis or known sensitivity to salicylates.

Population number of patients = 73.

Interventions Patients were randomised to either 5-aminosalicylic acid (5-ASA) 800 mg three times daily, or an identical placebo. Drug treatment was started 24 hours before EBRT and continued until 4 weeks after completion of EBRT. Due to differences in EBRT patients had duration of EBRT therapy ranging from 3 to 7 weeks.

Outcomes Diarrhoea, graded as none, mild, moderate and severe (0, 1, 2, 3 and 4). Patients were asked to complete a symptom questionnaire detailing bowel function at baseline and weekly during treatment.

Follow up Patients were seen by a doctor at least weekly during treatment

Results The severity of diarrhoea was significantly worse in the 5-ASA group.

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT	AMINOSALICYLATE (5-ASA)	PLACEBO	OVERALL RESULT
Diarrhoea	31/34, median severity was grade 2	28/38, median severity was grade 1	favours placebo (p=0.014) for severity, no sig. diff. in rate of diarrhoea (p=0.070)
Late radiation toxicity	major toxicity 1/34, minor toxicity 6/34	major toxicity 2/38, minor toxicity 4/38	

General comments -

(Henriksson *et al.* 1992)
Design: Randomized controlled trial (therapy), evidence level: 1+ Country: Sweden, setting: Secondary care **Inclusion criteria** 70 patients with carcinoma in the prostate or urinary bladder without distant metastases (T1-4No1xMo) and a performance status of greater than or equal to 90% on the Karnofsky scale. Radiotherapy was conventionally delivered with high-energy photons (four-field technique, the total dose 64 Gy, 2 Gy daily, total treatment time 5 to 6 weeks). Dose granules of sucralfate or placebo were dispensed to each patient 2 weeks after radiation started and continued for 6 weeks. **Exclusion criteria** - **Population** number of patients = 70. **Interventions** oral sucralfate or placebo **Outcomes** stool frequency, stool consistency, occurrence of blood and mucus in stools, weight decrement, abdominal pain **Follow up** weekly check up throughout the study Follow - up: 2 months after the end of the RT 12 months after the end of the RT **Results** During the investigation period, the frequency of defecation and stool consistency were significantly improved by sucralfate. Also, 14 patients in the placebo group and 3 in the sucralfate group required symptomatic therapy with loperamide, p=0.003. One year later, the patients in the sucralfate group displayed significantly less problems with frequency of defecation (p=0.01), and mucus in the stools (p=0.01) compared with

the placebo group. There was also a lower intake of loperamide, 9 patients in the placebo group and 4 in the sucralfate group, who required symptomatic therapy with loperamide, (p= 0.11) and the weight decrease was less pronounced in the sucralfate group (p=0.04). There was no evidence of adverse effects associated with the use of sucralfate.

COMPARISON IN PATIENTS WITH BOWEL DISCOMFORT AFTER PELVIC RADIOTHERAPY	SUCRALFATE	PLACEBO	OVERALL RESULT
rectal bleeding	During study period + 2 mth F/U: no difference 3/32. 1 year after RT: 4/28.	During study period + 2 mth F/U: no difference 5/34. 1 year after RT:9/28	During study period + 2 mth F/U: no significant difference between groups in bleeding. 1 year after RT: no significant difference between groups in bleeding
Diarrhoea	During study period + 2 mth F/U: frequency per day 0-2=13/32. 1 year after RT: frequency per day 0-2= 24/28.	During study period + 2 mth F/U: frequency per day 0-2 = 7/34. 1 year after RT: frequency per day 0-2= 14/28	During study period + 2 mth F/U freq of diarrhoea was lower in sucralfate group: p=0.04. 1 year after RT: p=0.01
Diarrhoea Score=Consistency/Diarrhoea frequency	During study period + 2 mth F/U: no change or small increase in frequency and consistency = 18/32. 1 year after RT: no difference score	During study period + 2 mth F/U: no change or small increase in score = 7/34. 1 year after RT: no difference score	During study period + 2 mth F/U: p=0.003. 1 year after RT: no significant difference score
loperamide consumption	During study period + 2 mth F/U: consumption use = 3/32	During study period + 2 mth F/U: consumption use = 14/34	During study period + 2 mth F/U: p=0.003
Stool Consistency	During study period + 2 mth F/U: Loose 3/32	During study period + 2 mth F/U: Loose 10/34	During study period + 2 mth F/U: p=0.04
Mucus in stools	During study period + 2 mth F/U: no difference. 1 year after RT:	During study period + 2 mth F/U: no difference. 1 year	During study period + 2 mth F/U the occurrence of mucus in stools: no significant difference. 1 year

	7/28	after RT: 16/28	after RT: p=0.01
weight decrement (kg)	During study period + 2 mth F/U: no difference. 1 year after RT: 0.7	During study period + 2 mth F/U: no difference. 1 year after RT: 2.3	During study period + 2 mth F/U: no significant difference. 1 year after RT there was a significant decrease in weight in placebo compared to sucralfate group, p=0.04

General comments The findings from this study suggest that sucralfate can be of beneficial value in diminishing bowel discomfort during treatment and, most importantly, sucralfate reduces the late bowel disturbances that follow radiotherapeutic treatment of pelvic malignancies.

It must be noted that the study was small, follow up time was only 12 months and the use of independent reports from endoscopic examination would have provided useful evaluation of sucralfate on rectal injury.

(Hovdenak *et al.* 2005)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: International

Inclusion criteria Patients scheduled for curative pelvic EBRT between 1999 and 2000. The authors also searched Medline (1990 to 2004) for RCTs using prophylactic sucralfate in this population, to include in a meta-analysis.

Exclusion criteria Significant current or previous gastrointestinal disease

Population -

Interventions EBRT was given as single daily doses of 2 Gy to 64 to 70 Gy, 5 days a week for 6.5 to 7 weeks. Patients were randomised to receive sucralfate 1g tablet twice daily or a placebo, starting on the first day of EBRT and continuing through the course of radiotherapy.

Outcomes Symptoms (abdominal pain, tenesmus, bloating and diarrhoea), doctors completed questionnaires at the follow up visits and patients kept symptom diaries. Endoscopic mucosal injury was scored on a 4 point scale (0-normal to 3-spontaneous haemorrhage or visible ulcers). Quantitative histology using mucosal biopsies obtained from the posterior rectal wall.

Follow up Symptoms were assessed before EBRT (week 0), and at 2, 4 and 6 weeks after the start of EBRT.

Results In the RCT grade 2 -3 diarrhoea was significantly greater in the sucralfate group at weeks 2 (p=0.049) and 4 (p=0.033). There were no other significant differences at any time point between the groups for any of the outcomes.

The meta-analysis of 6 RCTs did not show a significant effect of sucralfate on the rate of grade 2 to 3 diarrhoea.

COMPARISON IN PATIENTS RECEIVING RADICAL PELVIC EBRT	SUCRALFATE	PLACEBO	OVERALL RESULT
Diarrhoea (grade 2 to 3)	146/345 (6 RCTs combined)	157/358 (6 RCTs combined)	No sig. difference, OR=0.94 [95% CI 0.70 to 1.26]

General comments -

(Kozelsky *et al.* 2003)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: United States, setting: Tertiary care

Inclusion criteria Patients scheduled to receive whole pelvic EBRT for histologically confirmed cancer, at a North Central Cancer Treatment Group approved facility.

Exclusion criteria Pregnancy, allergy to glutamine, previous pelvic EBRT, inflammatory bowel disease, stool incontinence, prior abdominal perineal resection, or planned used of leucovorin or cytotoxic chemotherapy.

Population number of patients = 129.

Interventions The planned dose to the whole pelvic field was between 45 and 53.5 Gy, with a boost to the primary tumour or tumour bed where appropriate.

Patients were randomised to glutamine 4g (8mL) (twice daily) or placebo (glycine). Medication was made up to 40 mL of Ora-Sweet (Paddock Laboratories).

Outcomes Bowel toxicity according to the NCI common toxicity criteria. Patients also completed a bowel function questionnaire at each follow up visit. QOL was measured using the UNISCALE QOL measure.

Follow up At baseline and at weekly intervals during EBRT patients were evaluated by an oncologist or radiation therapy nurse who recorded toxicity. 12 month follow-up was 42/64 for the glutamine group and 44/69 for the placebo group. 24 month follow-up was 39/64 and 35/69 for the respective groups.

Results -

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT	GLUTAMINE	PLACEBO	OVERALL RESULT
Diarrhoea	51/64 had diarrhoea, median max. grade = 2	51/65 had diarrhoea median max. grade = 2	No sig. diff. for prevalence (p=0.99) or max. grade (p=0.76)
Abdominal cramping	Rate was 47/64, median max. grade = 1	39/64, median max. grade = 1	No sig. diff. for max. grade (p=0.31)
Tenesmus	Rate was 27/64, median max. grade = 0	Rate was 21/65, median max. grade = 0	No sig. diff. for max. grade (p=0.22)
Quality of life	mean was 80% at baseline, and 75% at	mean was 80% at baseline, and 75% at	No sig. diff.

	2 months	2 months

General comments -

(Martenson *et al.* 1996)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: United States, setting: Tertiary care

Inclusion criteria Patients with histologically confirmed cancer in the pelvis, without evidence of distant metastases, in whom a course of EBRT was planned. The EBRT treatment volume had to include the entire true pelvis, daily dose between 1.7 and 2.1 Gy to a total of between 45 and 53.5 Gy. Some patients had an EBRT boost to the tumour bed. Performance status 2 or less.

Exclusion criteria Non-functioning rectum. Stool incontinence or frequency of more than 6 stools daily. Cytotoxic chemotherapy (apart from 5-FU with or without levamisole). Patients with a history of prior pelvic EBRT, inflammatory bowel disease, salicylate therapy or intraluminal bowel tumours.

Population number of patients = 58.

Interventions Patients were randomised to receive either olsalazine (250 mg twice daily) or a placebo. Treatment with olsalazine continued until EBRT was complete, unless adverse effects were experienced (more than 7 stools per day above the baseline stool frequency).

Outcomes Primary endpoint was diarrhoea, with rectal bleeding, abdominal cramping and tenesmus as secondary endpoints. Toxicity outcomes were scored on a 0 to 4 scale (0 being no toxicity 4 being the worst), using National Cancer Institute Common Toxicity Criteria. Patients were evaluated weekly during EBRT.

Follow up The planned accrual was 300 patients, but the trial was stopped early when preliminary analysis showed excess diarrhoea in the experimental group.

Results The olsalazine group experienced more severe diarrhoea than the placebo group. The authors concluded that olsalazine is contraindicated in this group.

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT	AMINOSALICYLATE (OLSALAZINE)	PLACEBO	OVERALL RESULT
Diarrhoea	24/30, median grade was 3	21/28, median grade was 1	favours placebo ($p<0.01$, Wilcoxon test)

Abdominal cramping	16/30, median grade was 1	median grade was 0	favours placebo (p=0.084, Wilcoxon test)
Tenesmus	4/30, median grade was 0	11/25, median grade was 0	favours olsalazine (p=0.033, Wilcoxon test)
Rectal bleeding	8/30, median grade was 0	9/28, median grade was 0	no sig. diff. (p=0.595, Wilcoxon test)

General comments -

(O'Brien *et al.* 2002)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: Australia, setting: Secondary care

Inclusion criteria patients with localized prostate carcinoma

Exclusion criteria -

Population number of patients = 86.

Interventions a daily enema of 3g of sucralfate in a 15-mL suspension

Outcomes RTOG late toxicity score

Patient self assessment of a range of symptoms (frequency of bowel movement, diarrhoea or looseness of bowel motions, rectal pain, faecal urgency, rectal bleeding, change in toilet behaviour, overall effect on daily living and general bowel upset.)

Follow up median follow-up = 5 years

Results With a median follow-up of 5 years, the Kaplan-Meier probability of late Grade 2 RTOG/EORTC toxicity was 12% (95% CI 2-22%) for placebo and 5% (95% CI 0-12%) for sucralfate (p = 0.26). The probability of late rectal bleeding was 59% (95% CI 45-73%) for placebo and 54% (95% CI 40-68%) for sucralfate.

No statistically significant difference was found between the treatment arms for the peak incidence of any of the other patient self-assessment variables (frequency of bowel movement, diarrhoea or looseness of bowel motions, rectal pain, faecal urgency, rectal bleeding, change in toilet behaviour, overall effect on daily living and general bowel upset.).

Cox proportional hazards modelling indicated acute RTOG/EORTC toxicity of Grade 2 or greater was associated with a hazard ratio of 2.74 (95% CI 1.31-5.73) for the development of late toxicity of Grade 1 or greater. Substituting the patient self-assessment variables for acute

RTOG/EORTC toxicity revealed that rectal pain of a moderate or severe grade during RT was the best predictor of the subsequent development of late toxicity, with a hazard ratio of 3.44 (95% CI 1.68-7).

COMPARISON IN PCa PATIENTS TREATED WITH RT	SUCRALFATE (ENEMA)	PLACEBO (ENEMA)	OVERALL RESULT
RTOG grade score	The Kaplan-Meier probability of late Grade 2 RTOG/EORTC toxicity was 5% (95% CI 0-12%) for sucralfate (p = 0.26).	The Kaplan-Meier probability of late Grade 2 RTOG/EORTC toxicity was 12% (95% CI 2-22%) for placebo	No stat significant difference was reported in the Kaplan-Meier risk of either Grade 1 or 2 RTOG late rectal toxicity for either arm of study.
rectal bleeding	The probability of late rectal bleeding was 54% (95% CI 40-68%) for sucralfate.	The probability of late rectal bleeding was 59% (95% CI 45-73%) for placebo	No statistically significant difference was noted between the two arms

General comments Author's comments:

The results of this study do not support the use of sucralfate administered rectally as a method for reducing the late toxicity of non-conformal RT for prostate cancer. There appears to be an association between the development of acute and subsequent late toxicity, although the nature of this association remains to be determined.

(Resbeut *et al.* 1997)

Design: Randomized controlled trial (), evidence level: 1+

Country: France, setting: Tertiary care

Inclusion criteria Patients aged between 18 and 80 receiving radiotherapy for prostate or uterus cancer. Karnofsky performance index of 80 or more. Patients from 6 cancer centres were entered. 68.5% patients had prostate cancer and the remainder uterine cancer.

Exclusion criteria Concurrent chemotherapy, previous pelvic or abdominal radiotherapy, intestinal resection or colostomy, hypersensitivity to salicylates and prior diarrhoea.

Population number of patients = 153.

Interventions Pelvic radiotherapy consisted of 45 to 52 Gy in 4.5 to 5 weeks. After pelvic radiotherapy a tumour boost with EBRT or brachytherapy was delivered where appropriate.

Patients receiving EBRT maintained a low fibre and low lactose diet.

Patients were randomised to receive either mesalazine tablets 500mg (daily dose 4g) or placebo throughout the pelvic irradiation period.

Outcomes The primary endpoint was diarrhoea assessed using the WHO criteria: a scale ranging from 0 (absent) to 4 hemorrhagic diarrhoea or dehydration). Secondary endpoints were abdominal pain, weight loss and tolerance to drug treatments.

Follow up Symptoms were assessed daily using a patient self-questionnaire and weekly by the investigator during pelvic radiotherapy. The investigators also assessed symptoms 1 and 3 months after completion of EBRT. 34 patients were lost to follow up, 18/74 in the treatment group and 16/79 in the placebo group.

Results -

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT	AMINOSALICYLATE (MESALAZINE)	PLACEBO	OVERALL RESULT
Diarrhoea	51/74 (69%), median grade 2	52/79 (66%), median grade 1	No sig. diff. (p=0.22). Severity of diarrhoea did not differ between groups (p=0.14).
Diarrhoea (duration)	mean 22.7 days	mean 22.1 days	no sig. diff. (p=0.88)

General comments -

(Sherman *et al.* 1989)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: United States, setting: Tertiary care

Inclusion criteria Patients undergoing EBRT to the lower abdomen or pelvis. Patients had to have had at least five radiotherapy fractions before the onset of diarrhoea; three of more loose stools per day before start of antidiarrhoeal treatment. Age 18 years or more.

Exclusion criteria EBRT related diarrhoea. Cytotoxic chemotherapy. Known sensitivity to loperamide.

Population number of patients = 47.

Interventions EBRT was a minimum of 1000 rads over one week prior to the start of antidiarrhoeal treatment.

Patients received either loperamide 2mg capsules or an identical placebo. They were

instructed to take 2 capsules as initial therapy if they experienced 3 or more loose stools in a 24 hour period. From then on one capsule was to be taken after each loose stool, to a maximum of eight capsules. The duration of treatment was 7 days.

Outcomes Stool frequency per day. Stool consistency graded from 1 (normal) to 4 (watery). Related symptoms: cramps, nausea and vomiting. Patients recorded these outcomes in a diary, as well as the use of study and non-study medications. Side effects.

Follow up On the final day of treatment (day 7) the doctor and patient assessed the severity of related symptoms: cramps, nausea and vomiting. 5/47 patients were excluded from the analysis because of non-compliance with the medication.

Results Values for comparisons of stool frequency and consistency over the seven day treatment period were calculated as area under the curve by the trapezoidal rule. For stool consistency a score was calculated by multiplying the number of stools by the consistency score (1 to 4). One patient taking loperamide had nausea; in the placebo group skin rash and cramps each occurred in one patient

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT	ANTIMOTILITY DRUG (LOPERAMIDE)	PLACEBO	OVERALL RESULT
Stool frequency	Mean area under the curve of frequency vs. treatment day was 12.6	Mean area under the curve of frequency vs. treatment day was 19.1	favours loperamide (p=0.04, t-test)
Stool consistency	Mean area under the curve of frequency vs. treatment day was 26.6	Mean area under the curve of frequency vs. treatment day was 44.1	favours loperamide (p=0.02, t-test)

General comments -

(Vernia *et al.* 2000)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: Italy, setting: Tertiary care

Inclusion criteria 58 patients completed a cycle of EBRT to the pelvis, for prostate or cervical cancer, over a period of 13 months at one institution. 25 of this group developed radiation proctitis and 20 agreed to enter the study

Exclusion criteria -

Population number of patients = 20.

Interventions Patients were randomised to receive either a sodium butyrate enema (80 mL) or saline placebo enema (80mL) every day for three weeks. Patients were instructed to self administer the enema each night before sleeping. After 3 weeks patients crossed over to the other treatment arm.

Outcomes Bowel movement frequency and consistency, rectal bleeding, night bowel movements, abdominal pain, tenesmus. Histological and endoscopic grading.

Follow up Patients were assessed clinically, endoscopically and histologically before entry to the study, at 3 weeks and at the end of the study (6 weeks). 2/20 patients withdrew at 3 weeks, before crossing over to the alternative treatment arm.

Results -

COMPARISON IN PATEINTS WITH ACUTE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY	BUTYRATE	PLACEBO (ENEMA)	OVERALL RESULT
Stool Consistency	not reported	not reported	in favour of butyrate OR 40.5 [95% CI 3.1 to 529.2]
rectal bleeding	not reported	not reported	in favour of butyrate OR 17.9 [95% CI 1.6 to 194.8]
Abdominal pain	not reported	not reported	no sig. diff., OR 4.8 [95% CI 0.7 to 32.1]
Tenesmus	not reported	not reported	in favour of butyrate OR 16.5 [95% CI 1.5 to 181.3]
endoscopic grading	not reported	not reported	in favour of butyrate OR 10.4 [95% CI 0.9 to 114.2]

General comments Small trial

(Yavuz *et al.* 2002)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: Turkey, setting: Tertiary care

Inclusion criteria Patients with grade 2 or 3 diarrhoea (NCI common toxicity criteria) experienced during the 24-hour period after a fraction of pelvic radiotherapy. Patients had histological confirmed cancer in the pelvis, without evidence of distant metastases. ECOG performance status of 2 or less, and age 18 years or more.

Exclusion criteria Grade 4 diarrhoea. Chemotherapy, antibiotics or other medication that could interfere with the anti-diarrhoeal medication. History of gastrointestinal disorder known to cause diarrhoea. Active intraluminal tumour. Participation in another clinical trial.

Population number of patients = 61.

Interventions Patients were randomised to receive either octreotide acetate (Sandostatin) or co-phenotrope (diphenoxylate plus atropine sulfate, Lotomil). Octreotide was given in as a 100 microgram sub-cutaenous injection, three times daily. Co-phenotrope was given orally as a 2.5 mg tablet four times daily. All patients had antidiarrhoeal treatment for an initial 3 day period. Antidiarrhoeal treatment was stopped at 3 days if complete response was seen. Treatment was continued to 5 days if a partial response was seen. EBRT was discontinued at 3 days if no antidiarrhoeal response was seen.

Outcomes Response to treatment for diarrhoea, classed as complete, partial or none. Duration of diarrhoea, starting from the first day of treatment. Interruption period of pelvic radiotherapy. Patients recorded symptoms on each day of treatment.

Follow up Toxicity and compliance were assessed by medical and nursing staff every day during antidiarrhoeal treatment. All patients were assessable (no drop-out).

Results -

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT	SOMATOSTATIN ANALOGUE (OCTREOTIDE)	ANTIMOTILITY DRUG (CO-PHENOTROPE)	OVERALL RESULT
Diarrhoea duration	mean 3.3 days (SD 0.3 days)	mean 5.36 days (SD 0.4 days)	in favour of octreotide (p<0.001, t-test)
Diarrhoea	20/33 complete response to treatment	4/28 complete response to treatment	in favour of octreotide (p=0.002, Chi square test)
Interruption to radiotherapy	mean duration 0.45 days (SD 0.2 days)	mean duration 1.89 days (SD 0.5 days)	in favour of octreotide (p=0.003, Mann Whitney test)

General comments -

(Hille *et al.* 2005)

Design: Randomized controlled trial (therapy), evidence level: 1++

Country: Germany, setting: Tertiary care

Inclusion criteria Men with prostate cancer treated with radiotherapy to achieve local control.

Exclusion criteria Stage T4 cancer, more than 5 stools per day, history of inflammatory bowel disease, expected non-compliance

Population number of patients = 100, mean age = 68 years.

Interventions Patients were randomised to receive rectal suppositories of either misoprostol (200 micrograms of Cytotec) or placebo, one hour before each radiotherapy session. Pelvic EBRT to a dose of 45 Gy (1.8 Gy fractions), followed by a boost to the prostate (total dose 71 Gy). In the event of grade 2 symptomatic proctitis, suppositories were stopped and sodium butyrate enemas applied. If there was still no relief corticosteroids were used.

Outcomes Radiation induced toxicities, graded using the NCI common toxicity criteria.

Follow up A radiation oncologist evaluated radiation induced toxicity every week during the EBRT. One patient withdrew from the study due to difficulties inserting the suppositories.

Results Rectal bleeding was significantly worse in the misoprostol group. Five patients experienced mild faecal urgency due to the suppositories.

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT	MISOPROSTOL	PLACEBO	OVERALL RESULT
Proctitis	none 24%; grade 1 , 76%; grade 2, 36%	none 24%; grade 1 , 76%; grade 2, 26%	No significant difference in incidence or severity
Tenesmus	52%	32%	No significant difference
rectal bleeding	32%	14%	favours placebo (p=0.03)
Stool frequency	60% had increased frequency	68% had increased frequency	No significant difference

General comments -

(Chary & Thomson 1984)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: Canada (federal state, Commonwealth Realm), setting: Secondary care

Inclusion criteria patients with primary diagnosis or cancer of cervix, gynaecological region, prostate, performance status= 0-1 ECOG scale.

Exclusion criteria Pt with pre-existing gastrointestinal problems who had undergone intestinal surgery, colostomy and previous chemo or RT were excluded.

Population number of patients = 32, mean age = 68 years.

Interventions 40 gm fat diet +/- cholestyramine

Outcomes Diarrhoea scale: frequency, consistency recorded in a patient diary which was then converted into a diarrhoea scale.

Adverse effects

Follow up 2 months

Results A total of 35 patients receiving pelvic irradiation were entered in the study and all patients had received a 40 gm fat diet. The group was then randomized to receive either placebo (17 patients) or cholestyramine (18 patients). Diarrhoea occurred in 6 out of 16 evaluable patients in the control group and only 1 of the 17 evaluable patients in the cholestyramine group.

The frequency of diarrhoea and the diarrhoea scale remained high in the placebo group in the entire observation period. Statistical analysis had revealed better diarrhoea control in the cholestyramine group (p = <0.05).

The adverse effects associated with the use of cholestyramine are nausea, and abdominal cramps.

COMPARISON IN PATIENTS RECEIVING PELVIC RADIOTHERAPY	LOW FAT DIETS FOLLOWED BY CHOLESTRYAMINE	LOW FAT DIETS FOLLOWED BY PLACEBO	OVERALL RESULT
Diarrhoea scale			At week4, 6 &7 after start of RT statistical significant difference, in favour of cholestyramine group was found, p=0.05. The difference from the time of admin of treatment for both groups was

			statistically significant, p=0.05
Adverse effects	9/17 reported 12 adverse effects, 6 of these required medication to suppress symptoms.	nausea and abdominal cramps, 2/16 evaluable pts	All adverse effect in both groups were transient and none had persisting symptoms at the end of the trial
Diarrhoea scale			Using an ANOVA of the weekly diarrhoea scale measurements from the time of the test medication was started, a stat significant difference between groups was reported p=0.05

General comments. It was concluded that cholestyramine is effective in preventing acute diarrhoea induced by pelvic irradiation in patients receiving a low fat diet but is associated with side effects.

(Coleman *et al.* 2002)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: United States, setting: Tertiary care

Inclusion criteria Patients with histologically proven prostate cancer receiving EBRT. Urinary function and bowel function were assessed at baseline using a questionnaire. Patients had to show worsening of urinary or bowel symptoms during EBRT to be eligible for the study. Creatinine clearance of more than 50 mL/min. Accrual to the trial was stopped early because the principal investigator left.

Exclusion criteria Patients already taking NSAIDs or aspirin. Prostatectomy, lactose intolerance, peptic ulcer disease, anticoagulation therapy, congestive heart failure. Concurrent use of drugs that could interfere with ibuprofen.

Population number of patients = 53.

Interventions Patients were randomised to 7 days of either ibuprofen (400 mg 4 times daily) or placebo.

Outcomes Patients had a single score for urinary symptoms (7 categories each 1-4) ranging from 7 (best) to 28 (worst). Patients had a single score for bowel symptoms (6 categories each 1-4) ranging from 6 (best) to 24 (worst). Symptoms were assessed by questionnaire at each radiotherapy visit.

Follow up The symptom survey was conducted 1 week after randomisation. 4/53 patients were missing data and the investigators excluded them from the analysis.

Results below show the median change in the symptom scores, from the time of randomization to 1 week after the start of study treatment. A positive value indicates worsening of symptoms.

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT FOR PROSTATE CANCER	NSAID (IBUPROFEN)	PLACEBO	OVERALL RESULT
gastrointestinal symptoms	median change after treatment +2 (range -2 to +12)	median change after treatment +2 (range -2 to +7)	difference was not significant (p=0.74, Wilcoxon test)

General comments -

(Ehrenpreis *et al.* 2005)

Design: Randomized controlled trial (therapy), evidence level: 1-

Inclusion criteria pt who had received EBRT or brachytherapy and had symptoms of chronic radiation proctopathy.

Exclusion criteria pts who were treated for anaemia. Also, if they had rectal ulceration, stricture or fistulisation or significant liver disease or unable to sign consent form.

Population number of patients = 17.

Interventions oral retinol palmitate (vitamin A), 10 000 IU

Outcomes The Radiation Proctopathy System Assessments Scale (RPSAS) score. The RPSAS was used to measure symptoms of proctopathy: diarrhoea rectal urgency, rectal pain, tenesmus, rectal bleeding faecal incontinence.

Follow up 90 days

Results Seven of ten retinol palmitate (Vitamin A) patients responded, whereas two of nine responded to placebo (P = 0.057). Mean pre-post-treatment change in Radiation Proctopathy System Assessments Scale in the Vitamin A group was 11 +/- 5, compared to the placebo group which was 2.5 +/- 3.6 (P = 0.013). All five placebo non-responders who were crossed over to treatment with retinal palmitate responded to treatment.

See PICO

COMPARISON IN PATIENTS RECEIVING RADICAL PELVIC EBRT	VITAMIN A	PLACEBO	OVERALL RESULT
RPSAS score	11+/-5	2.5+/- 3.6	The mean pre-post treatment change in RPSAS in Vitamin A group was significantly to different to placebo group, p=0.013
response to Vitamin A	7/10	2/9	A trend toward a significant difference was observed in favour of responding to Vitamin A (P = 0.057).
RPSAS score	25 baseline and 17 after 90 days		5 placebo non responders crossed over to Vitamin A group, a significant difference in the RPSAS scores was observed, p<0.05

General comments Author's note:

This trial evaluated retinol palmitate and found that it significantly reduced rectal symptoms of radiation proctopathy, perhaps because of wound-healing effects. The current results can serve as the foundation for future trials examining retinol palmitate in the multi-institutional setting

(Freund *et al.* 1987)

Design: Randomized controlled trial (), evidence level: 1-

Country: , setting: Tertiary care

Inclusion criteria Patients receiving radiotherapy for prostate cancer

Exclusion criteria -

Population number of patients = 16.

Interventions Patients were randomised to receive mesalazine as suppositories (250 mg 3 times a day) or placebo.

Outcomes Radiation induced proctitis

Follow up Trial stopped early due to an excess of proctitis in the mesalazine group.

Results -

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT FOR PROSTATE CANCER	AMINOSALICYLATE (MESALAZINE)	PLACEBO	OVERALL RESULT
Proctitis	6/8	1/8	

General comments German language paper, only appraised the English abstract

(Hombrink *et al.* 1995)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: Germany, setting: Tertiary care

Inclusion criteria Patients receiving pelvic EBRT for pelvic malignancy at one of three centres between 1992 and 1993.

Exclusion criteria -

Population number of patients = 174.

Interventions Patients were randomised to receive smectite (Skilpin) at the beginning of EBRT or to standard care, where diarrhoea was treated using antimotility drugs when it appeared.

Outcomes Incidence of diarrhoea and tenesmus.

Results -

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT	SMECTITE	STANDARD CARE	OVERALL RESULT
Diarrhoea	30/80 (37.5%)	63/94 (67%)	RR = 0.56 [95% CI 0.41 to 0.77], NNT = 3.39 [95% CI 2 to 7]
Tenesmus	20/80 (25%)	41/94 (44%)	RR = 0.57 [95% CI 0.34 to 0.89], NNT = 5.37 [95% CI 3 to 21]

General comments German language, only the English abstract was appraised.

(Jahraus *et al.* 2005)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: United States, setting: Tertiary care

Inclusion criteria Patients scheduled to receive EBRT for histologically confirmed prostate cancer, stage T1 to T3, M0. Some patients (around 15%) received EBRT for biochemical recurrence after prostatectomy. Dose was at least 45 Gy to the pelvis and 64 Gy to the prostate. Age 18 years or more.

Exclusion criteria Prior history of pelvic or abdominal radiation, stool incontinence, stool frequency of more than 6 per day, history of irritable bowel symptom, known salicylate sensitivity, and current or prior use of any 5-ASA drug.

Population number of patients = 27, mean age = 67 years.

Interventions Patients were randomised to either balsalazide 700 mg or placebo (both 3 capsules 2 times a day). Drug therapy started before EBRT and continued daily until 14 days after completion of EBRT.

Outcomes Proctitis, diarrhoea, dysuria and fatigue Patients were assessed by doctors every week and toxicities rated using the NCI Common Toxicity Criteria version 2.0. A toxicity index was calculated by multiplying the grade of the toxicity by the number of days it was experienced, and adding the results.

Follow up Dropout rate was 3/15 in the treatment group and 1/13 in the control group.

Results -

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT FOR PROSTATE CANCER	AMINOSALICYLATE (BALSALAZIDE)	PLACEBO	OVERALL RESULT
Proctitis	mean toxicity index score 35.3	mean toxicity index score 74.1	favours balsalazide (p = 0.04)
Diarrhoea	mean toxicity index score 29.8	mean toxicity index score 40.7	difference not significant (p value not reported)
Dysuria	mean toxicity index score 31.4	mean toxicity index score 53.8	difference not significant (p value not reported)

Fatigue	mean toxicity index score 28.9	mean toxicity index score 41.8	difference not significant (p value not reported)

General comments Small trial. The authors' toxicity index makes it impossible to differentiate severe toxicity of short duration with mild toxicity of long duration.

(Khan *et al.* 2000)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Patients who had pelvic EBRT with curative intent, for stage B or C prostate cancer at a single institution. 8 patients had EBRT only and 8 EBRT plus brachytherapy.

Exclusion criteria Chronic diarrhoeal illness, prior pelvic radiotherapy or prior rectal bleeding.

Population number of patients = 16, age range 51 to 77 years.

Interventions Patients were randomised to receive either a misoprostol (400 micrograms, Cytotec) or a placebo rectal suppository 1 hr before each EBRT session. Treatment continued for the duration of EBRT.

Outcomes Radiation proctitis, using the institutions own scale - the 12 point radiation proctitis symptom score. The score grades stool frequency, rectal tenesmus (or abdominal cramps), rectal bleeding and general well being on a scale of 0 to 3 where 0 is best and 3 is worst. The scores on each symptom are combined to give an overall proctitis score.

Acute proctitis was defined as occurring 1 to 3 months after start of EBRT, and chronic proctitis as occurring 9 months after start of EBRT.

Follow up An investigator rated each patient on the proctitis scale at baseline, and at 1, 2, 3 and 9 months after the start of EBRT.

Results -

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT FOR PROSTATE CANCER	MISOPROSTOL	PLACEBO	OVERALL RESULT
Acute proctitis	mean (95% CI) scores at 1,2 and 3 months were 0.78 (-0.2 to 1.8), 0.67 (-0.2 to 1.5) and 0.33	mean (95% CI) scores at 1,2 and 3 months were 4.86 (3.1 to 6.7), 5.86 (4.1 to 7.6) and 5.71	in favour of misoprostol at each time point (p<0.01)

	(-0.1 to 0.7)	(4.0 to 7.5)	
Chronic proctitis	at 9 months mean (95% CI) was 0.37 (-0.1 to 0.8)	at 9 months mean (95% CI) was 3.86 (0.9 to 6.8)	in favour of misoprostol (p<0.01)

General comments Underpowered trial. More brachytherapy in the placebo group

(Martin *et al.* 2002)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: Germany, setting: Tertiary care

Inclusion criteria Indication for pelvic EBRT after macroscopically complete resection of a pelvic malignancy. Age 18 years or older. Karnofsky performance status of 90 or more. A single prostate cancer patient was included. Patients were enrolled between 1994 and 1997.

Exclusion criteria Palliative EBRT, colostomy, intolerance to proteolytic enzymes, participation in other clinical trials.

Population number of patients = 56.

Interventions Patients were randomised to either proteolytic enzyme treatment or to placebo, starting 3 days before EBRT until the end of EBRT treatment. The proteolytic enzyme consisted of capsules containing 100 mg papin, 40 mg trypsin and 40 mg chymotrypsin.

Outcomes Toxicity: diarrhoea, nausea, vomiting, fatigue and epitheliolysis. Toxicities were scored on 5 point scales derived from the NCI common toxicity criteria and the RTOG acute radiation morbidity criteria.

Follow up Baseline evaluation was done at 3 days before radiotherapy. Toxicity assessments were made by the oncologist at 3, 8, 15, 21, 28 and 35 days after the start of radiotherapy. Three patients in each treatment group dropped out of the study within the first 2 weeks of treatment, and one patient in each group dropped out after 3 weeks.

Results There was no significant difference in acute radiation toxicity between the two groups.

COMPARISON IN PATIENTS RECEIVING RADICAL PELVIC EBRT	PROTEOLYTIC ENZYMES	PLACEBO	OVERALL RESULT
Diarrhoea	12/28 mild or no diarrhoea, 16/28 moderate or severe	18/28 mild or no diarrhoea, 10/28 moderate or severe	No sig. diff. (p=0.11, Chi square)

Nausea	2/28 had moderate or severe nausea	2/28 had moderate or severe nausea	No sig. diff. (Fishers exact test)
Vomiting	0/28 had moderate or severe vomiting	1/28 had moderate or severe vomiting	
Fatigue	5/28 had moderate or severe fatigue	2/28 had moderate or severe fatigue	No sig. diff. (p=0.23, Chi square)
Epitheliolysis	7/28 had moderate or severe epitheliolysis	3/28 had moderate or severe epitheliolysis	No sig. diff. (p=0.16, Chi square)

General comments -

(Murphy *et al.* 2000)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: United Kingdom

Inclusion criteria Pt with PCa and gynaecological cancer who were undergoing radiotherapy to the pelvis of at least 4000cGy in 20 fractions were recruited.

Exclusion criteria Pt with a history of gastrointestinal disease or who had regular use of laxatives or diarrhoea medication were excluded.

Population number of patients = 60, age range 46 to 79 years.

Interventions Metamucil

Outcomes The Murphy Diarrhoea Scale was developed to assist in the synthesis of data collected in daily patient-reported diaries.

Follow up approximately 28 days post treatment

Results were analyzed for the presence of radiation-induced diarrhoea in two groups: patients taking Metamucil (n = 30) or not taking Metamucil (n = 30).

Results were analyzed using ANOVA F-tests.

Metamucil significantly decreased the incidence (p = 0.049) and severity (p = 0.030) of diarrhoea and showed a strong trend in reducing the use of diarrhoea medication (p = 0.062). According to this pilot study, Metamucil was an effective method of controlling radiation-induced diarrhoea

COMPARISON IN PATIENT WHO HAVE RECEIVED PELVIC	METAMUCIL	STANDARD CARE	OVERALL RESULT

RADIOTHERAPY			
Diarrhoea	1.8	2.33	There was a significant difference between groups on average severity score of diarrhoea (p=0.03)
Use of medication for diarrhoea	6.7%	15.1%	The mean % days for use of anti diarrhoeals showed a trend toward reduction in the Metamucil group, p=0.062
Diarrhoea	60%	83%	Incidence of diarrhoea was significantly decreased in the Metamucil group, p= 0.049
Radiation Induced Diarrhoea	13.9	14.1	Average time till onset of RID was similar in both groups, p=0.895
Radiation Induced Diarrhoea	41.5	38.5	Average duration of RID, was similar in both groups, p=0.905

General comments The scoring instrument, Murphy diarrhoea Scale (used to measure severity of diarrhoea has not been validated

Side Effects: none reported by patients.

(Stryker *et al.* 1983)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: United States, setting: Tertiary care

Inclusion criteria Patients receiving whole pelvic EBRT for pelvic malignancy.

Exclusion criteria -

Population -

Interventions Patients were randomised to either colestipol hydrochloride (in 5g packets) or to standard care. Both groups received diphenoxylate hydrochloride if they required symptomatic therapy for diarrhoea. Patients in the standard care group could also have atropine sulfate for diarrhoea.

The duration of pelvic radiotherapy ranged from 33 to 46 days.

Outcomes Stool frequency, nausea, vomiting, cramps and use of diphenoxylate hydrochloride for diarrhoea.

Follow up Each week during radiotherapy patients were given a questionnaire on which they recorded the outcome measures. 8 patients discontinued use of the drug to adverse effects.

Results There appeared to be significantly more nausea in the colestipol group, although the authors did not make a statistical comparison.

COMPARISON IN PATIENTS RECEIVING RADICAL PELVIC EBRT	ANION-EXCHANGE RESIN (COLESTIPOL)	STANDARD CARE	OVERALL RESULT
Stool frequency	baseline: mean 13.2 (SD 4.9) stools per week; at 6 weeks: mean 21.9 (SD 1.3)	baseline: mean 12.4 (SD 6.8) stools per week; at 6 weeks: mean 23.5 (SD 19.8)	no statistical comparison reported
Abdominal cramping	6/15	rate not reported	no statistical comparison reported
Nausea	11/15	4/16	no statistical comparison reported (but p<0.01, chi square)
Use of diphenoxylate for diarrhoea	baseline: mean 0 (SD 0) tablets per week; at 6 weeks: mean 11.1 (SD 14.2)	baseline: mean 0.4 (SD 1.8) tablets per week; at 6 weeks: mean 6.1 (SD 10.6)	no statistical comparison reported
Vomiting	4/15	2/16	no statistical comparison reported

General comments -

Prospective cross sectional study

(Gami *et al.* 2003)

Design: Prospective cross sectional study (therapy), evidence level: 3

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Patients attending a follow up clinic at the Royal Marsden Hospital, at least 1 year after completion of EBRT for cancer of the anus, rectum, bladder, prostate or gynaecological tract. Results for prostate cancer are presented separately (n=33).

Exclusion criteria -

Population number of patients = 107.

Interventions The patients with prostate cancer had received conformal EBRT to doses between 64 and 74 Gy in 2 Gy fractions

Outcomes Presence of gastrointestinal symptoms, the severity of the symptoms, and the impact of each symptom on quality of life. Measured using a questionnaire developed at the institution.

Follow up Patients were questioned at least one year after completion of EBRT.

Results -

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT	STANDARD EBRT	OVERALL RESULT
rectal bleeding	8/33	2/33 (6%) said bleeding affected their QOL
faecal incontinence	10/33	6/33 (18%) said the incontinence affected their QOL
Abdominal pain	6/33	6/33 (18%) said the pain affected their QOL
Diarrhoea	17/33	16/33 (48%) said diarrhoea affected their QOL
Tenesmus	4/33	
Flatulence	7/33	

General comments -

Systematic review of combined study designs

(Denton *et al.* 2002)
Design: Systematic review of combined study designs (therapy), evidence level: 1+ Country: , setting: Community **Inclusion criteria** The systematic review includes studies that have met the following criteria: Randomised controlled trials. Quasi-randomised trials, Cohort studies where the comparability of cohorts has been established or existing confounding factors adjusted (these studies may be prospective, or retrospective), case control studies, longitudinal surveys or case histories. Studies published in any language were included. All identified trials, published and unpublished were eligible. Patients must: have been diagnosed with a pelvic malignancy; all have undergone pelvic radiotherapy; must have subsequently developed late radiation complications which must include radiation proctitis of any grade, continuing from completion of radiotherapy for more than three months, or occurring more than three months after completionof radiotherapy. **Exclusion criteria** Any intervention that was prophylactic or patient group that did not have late proctitis from pelvic RT. **Interventions** ANTI INFLAMMATORY AGENTS RCTs: Kochlar 1991, Rougier 1992, Cavcic 2000 Non-randomised studies: Triantillidis 1990, Baum 1989, Goldstein 1976, Wurzer 1998 SHORT CHAIN FATTY ACIDS (SCFA) RCTs: Talley 1997, Pinto 1999

SUCRALFATE AND SIMILAR AGENTS

RCT: Kochlar 1991

Prospective studies : Kochlar 1999, Grigsby 1990 (population not men, very small studies and only 1study on PPS)

FORMALIN THERAPY

3 Prospective studies and 12 retrospective studies

3.6 to 4% or 10% formalin solution, direct application of gauzes soaked in formalin.

THERMAL COAGULATION Treatment

RCT: Jenson 1997

I prospective study and 14 retrospecive studies

HYPERBARIC OXYGEN THERAPY

No RCTs only observational studies

MISCELLANEOUS INTERVENTIONS (DILATORS, SUPEROXIDE DISMUTASE AGENTS, ANTI-FIBROTIC)

No RCTs

3 Case Series studies: (dilaters or stents)

Outcomes ANTI INFLAMMATORY AGENTS

RCTs:

Kochlar 1991, Rougier 1992, Cavcic 2000 (see PICO results)

Non-randomised studies:

Triantillidis 1990, Baum 1989, Goldstein 1976, Wurzer 1998 (see PICO results)

SHORT CHAIN FATTY ACIDS (SCFA)

RCTs: Talley 1997, Pinto 1999 (see PICO results)

SUCRALFATE AND SIMILAR AGENTS

RCT: Kochlar 1991 (see PICO results)

Prospective studies : Kochlar 1999 (no men), Grigsby 1990

FORMALIN THERAPY (see PICO result)

THERMAL COAGULATION Treatment

RCT: Jenson 1997 and other study types (see PICO)

I prospective study and 14 retrospecive studies (see PICO)

HYPERBARIC OXYGEN THERAPY

No RCTs only observational studies

resolution of symptoms (see results)

MISCELLANEOUS INTERVENTIONS (DILATORS, SUPEROXIDE DISMUTASE AGENTS, ANTI-FIBROTIC)

Strictures

Results ANTI INFLAMMATORIES

Side effects: Kochlar 1991: In 2 patients in anti-inflammatory group were excluded because of myalgia, nausea and headaches.

Quality of Life:

Kochlar 1991: no QoL assessment made.

No treatment related mortality was recorded. No studies were

identified which used quality of life measurements as a gauge of response to the intervention.(Triantillidis 1990, Baum 1989, Goldstein 1976, Wurzer 1998)

SCFA

No side effects were reported and there was no quality of life assessment.

FORMALIN Treatment

Side Effects: Anal ulceration, two rectal strictures, two patients with faecal incontinence and two with anal pain. (few cases only)

QoL: not collected

THERMAL COAGULATION Treatment

Side Effects: Recorded and none to report.

QoL: From informal reports patients reported an improvement in rectal bleeding and tenesmus and general health (due to controlled bleeding)

HYPERBARIC OXYGEN THERAPY

From the studies reviewed the impression is that HBO may be of value for large bowel chronic radiation changes that are refractory to other treatments, the degree of benefit and the cumulative effect or duration of response cannot be quantified from these reports because of the methodology and quality of the data.

QoL: no comment possible

Side Effects: Largely transient, minor and related to baro-trauma.

MISCELLANEOUS INTERVENTIONS (DILATORS, SUPEROXIDE DISMUTASE AGENTS, ANTI-FIBROTIC)

Although the strictures are described they are not scored and the absence of a formal baseline assessment and objective response means that the effect which is beneficial in each report cannot be quantified, nor can a comment on the duration of response be determined from the data available.

Side effects: variable in each report, including one case of brief post dilatation bowel pain and another case of post dilatation perforation.

QoL: (one report) the patients' general health was felt to improve because of the treatment.

COMPARISON IN PATIENTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY, 37 PATIENTS	SUCRALFATE	ANTI-INFLAMMATORY: PREDNISOLONE AND SULFASALAZINE	OVERALL RESULT
effect on clinical features	16/17 had an effect	8/15	In favour of sucralfate. OR for clinical improvement = 14.0 (CI =1.46-134.26)
endoscopic improvement	12/17	7/15	Sucralfate showed a trend toward improvement compared to anti-inflammatory group. OR =2.74 (CI=0.64-11.76), not significant different.
COMPARISON IN PATIENTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY (NO MEN WITH PCa), 32 PATIENTS	BETAMETHASONE ENEMA	HYDROCORTISONE ACETATE (90MG MOUSSE)	OVERALL RESULT
bowel activity	no findings reported	no findings reported	
rectal bleeding	3/14	6/16	the degree of bleeding was reduced but it was statistically significantly different, OR 2.20 CI=0.43-11.2
tenesmus	no findings reported	no findings reported	
COMPARISON IN	BETAMETHASONE ENEMA	HYDROCORTISONE ACETATE	OVERALL RESULT

PATIENTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY (NO MEN WITH PCa) , 32 PATIENTS		(90MG MOUSSE)	
endoscopic grading	5/14	12/16	A greater proportion of patients in the hydrocortisone group had endoscopic appearance improvement than in betamethasone group, OR 5.40 (CI=1.12-26.05)
COMPARISON IN PATIENTS WITH CHRONIC RADIATION PROCTITIS (60 CYTOLOGICALLY PROVEN PCa PATIENTS)	METRONIDAZOLE (ORAL) AND MESALAZINE (ORAL) AND BETAMETHASONE ENEMA	MESALAZINE (ORAL) AND BETAMETHASONE ENEMA	OVERALL RESULT
rectal bleeding and mucosal ulcers	Rectal bleeding and mucosal ulcers was significantly lower in the Metronidazole group. At 4 weeks (p=0.009), 3 months (p=0.031), 12 months (p=0.029)		Rectal bleeding and mucosal ulcers was significantly lower in the Metronidazole group.
rectal bleeding	One year after treatment: 22/24 demonstrated a reduction in the grade of rectal bleeding	5/12	OR = 15.40 CI=2.43-97.68, indication that favours treatment with Metronidazole, mesalazine and betamethasone.
diarrhoea and oedema	A significant decrease in this group after treatment at 4 weeks (p=0.044), 3 months (p=0.045) and 12 months (p=0.034)		A significant decrease in Metronidazole group after treatment at specific time points indicated.
diarrhoea and erythema	23/24 experienced reduction in	8/12	OR = 11.50 CI= 1.11-118.71, favouring treatment with the

	diarrhoea and rectal erythema		Metronidazole combination.
degree of rectal ulceration	The degree of rectal ulceration at 1 year had decreased		
in 22/24 of the Metronidazole group	7/12	7.86 CI= 1.24 to 49.84, favoured the use of Metronidazole.	
COMPARISON IN PATEINTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY	5 ASA ENEMAS	BETAMETHASONE ENEMA	OVERALL RESULT
reduction in symptoms of chronic radiation proctitis			No significant benefit for either treatment.
COMPARISON IN PATEINTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY	5 ASA ENEMAS	OVERALL RESULT	
reduction in symptoms of chronic radiation proctitis/colitis		5-ASA enemas do not appear to be effective in the treatment of radiation proctitis	
COMPARISON IN PATEINTS WITH CHRONIC RADIATION PROCTITIS AFTER PELVIC RADIOTHERAPY (15 PATIENTS TOTAL, 12 PCa)	SHORT CHAIN FATTY ACID ENEMA	PLACEBO (ENEMA)	OVERALL RESULT
symptom scores (symptoms = rectal bleeding, rectal pain, quantity of blood, days of			Symptom scores improved slightly on the active treatment (mean score 3.5 [range 3-5])

diarrhoea, number of stools and urgency)			compared with 4.5 mean score [range 3-6] for placebo group. Changes in the symptom score or changes in the individual
Symptoms were not statistically significant.			
COMPARISON IN PATEINTS WITH CHRONIC RADIATION PROCTITIS AFTER PELVIC RADIOTHERAPY (19 PATIENTS TOTAL, 1 MALE, DISEASE?)	SHORT CHAIN FATTY ACID ENEMA	PLACEBO (ENEMA)	OVERALL RESULT
# of days of rectal bleeding,	At 5 weeks 4.4 to 1.4 reduction in days per week of bleeding p=0.001. At the end of treatment period, 1.4 days of bleeding/wk	5.1 to 3.4, p=0.12. At end of treatment period, 3.4 days.	At 5 weeks a reduction of days/week of bleeding in SCFA p=0.001. At the end of treatment period, the weighted mean diff was -2 (-4.4 to -0.4), stat non sig. difference between groups.
colonoscopic score	At the end of the treatment period, the scores were similar in both groups. Endoscopic scores reduced by 2.6 (mean change 4.8 to 2.2) for SCFA.	At the end of the treatment period, mean change of 1.6 (5.7 to 4.1) for placebo group	At the end of treatment the Colonoscopic scores reduced in both arms but was significantly lower in SCFA p=0.02. The weighted mean difference was 1 (-2.33 to 4.33) showing a stat non sig. difference between SCFA and placebo.
DNA and protein content	At the end of the treatment period 13.1g/dl+/- 0.9	At the end of the treatment period, 10.7+/- 2.1g/dl	At the end of the treatment period Hb levels were higher in the SCFA group compared to

			the placebo group.
COMPARISON IN PATEINTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY	3.6 TO 4% OR 10% FORMALIN SOLUTION	OVERALL RESULT	
Any benefit from formalin in chronic haemorrhagic proctitis		No statistical analysis available between studies, however a general benefit was reported for the use of formalin.	
COMPARISON IN PATEINTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY	ENDOSCOPIC BIPOLAR ELECTROCOAGULATION	HEATER PROBE	OVERALL RESULT
rectal bleeding			The weighted mean difference was not significant
cant difference between the two treatments with regards to episodes of bleeding ,WMD 0.30 (CI= -0.35			
To 0.95).			
COMPARISON IN PATEINTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY	ENDOSCOPIC BIPOLAR ELECTROCOAGULATION	STANDARD MEDICAL TREATMENT FOR RECTAL BLEEDING	OVERALL RESULT
rectal bleeding	75% reduction	33%	

COMPARISON IN PATEINTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY	HEATER PROBE	STANDARD MEDICAL TREATMENT FOR RECTAL BLEEDING	OVERALL RESULT
rectal bleeding	67% reduction	11%	
units of blood transfused		greater reduction in units of blood	Use of the heater probe was associated with a greater reduction in the units of blood transfused than for the bipolar probe WMD-3.2 CI= -4.58 - -1.82
haematocrit		significantly greater	The increase in the haematocrit was significantly greater for the heater probe compared to the bipolar probe, WMD -2.90 CI= -5.22 - -0.58
COMPARISON IN PATEINTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY	THERMAL COAGULATION TREATMENT	OVERALL RESULT	
Any benefit to treat haemorrhagic proctitis		It appears from observational studies that thermal coagulation therapy has a useful role in haemorrhagic radiation proctitis that is refractory to other treatments in an attempt to avoid surgery. No statistical analysis can be made due to low quality.	
COMPARISON IN PATEINTS WITH LATE	HYPERBARIC OXYGEN THERAPY	OVERALL RESULT	

RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY		
Complete resolution of problem		From the studies reviewed the impression is that HBO may be of value for large bowel chronic radiation changes that are refractory to other treatments, the degree of benefit and the cumulative effect or duration of response cannot be quantified from these
COMPARISON IN PATEINTS WITH LATE RADIATION PROCTITIS AFTER RADICAL PELVIC RADIOTHERAPY	DILATORS	OVERALL RESULT
Strictures		No overall comment can be made due to low quality studies

General comments Rectal sucralfate showed greater clinical improvement for proctitis than anti-inflammatories (odds ratio (OR) 14.00, CI 1.46 to 134.26; n=1 study), though no difference was seen for endoscopic improvement (OR 2.74, CI 0.64 to 11.76, n=1 study).

The addition of Metronidazole to the anti-inflammatory regime also appeared to improve the response rate, as measured by reduction in rectal bleeding, diarrhoea, erythema and ulceration (n=1 study). Similarly rectal hydrocortisone appeared to be more effective than rectal betamethasone for clinical improvement although no difference was seen in endoscopic improvement (n=1 study).

Short chain fatty acid enemas did not appear to be effective compared to placebo (n=2 studies).

Comparing the heater probe and bipolar electrocautery (n=1 study), there was no discernible difference for severe bleeding after one year, but the heater probe demonstrated a greater increase in the haematocrit and reduced transfusion requirements.

(McGough *et al.* 2004)
Design: Systematic review of combined study designs (therapy), evidence level: 2++ Country: , setting: Other **Inclusion criteria** studies included gynaecological, rectal, urological patients and measured acute and chronic gastrointestinal toxicity to pelvis RT, while intervening with nutrition to alleviate side effects and/or assessed nutritional status of patients before start of or during a course of pelvic RT. **Exclusion criteria** - **Population** number of patients = 2646. **Interventions** therapeutic nutritional interventions: 1. dietary modifications during pelvis radiotherapy 2. dietary modifications after pelvic radiotherapy **Outcomes** Primary: bowel toxicity (measured using RTOG scale), other surrogate indicators: stool frequency and consistency, record of use diarrhoea medication, patient reported gastrointestinal symptoms Secondary: nutritional status assessed by change in weight, other anthropometric indicators, changes in dietary intake **Follow up** Varied among studies **Results** A total of 36 papers published in peer-reviewed journals between 1966 and 2003 were identified. In all, 14 randomised controlled trials, 12 prospective cohorts, four retrospective, two qualitative, one validation, one pilot study and two case reports were obtained. These included 2646 patients. Eight articles including three conference abstracts and web-based information were found.

None of the studies was definitive because of weakness in methodology.

There is a limited and varied evidence base for the use of nutritional interventions to prevent or manage bowel symptoms attributable to radiotherapy.

COMPARISON IN PATIENTS RECEIVING PELVIC RADIOTHERAPY	LOW FAT DIETS	UNRESTRICTED FAT INTAKE DIET/LOW FAT DIET	OVERALL RESULT
Diarrhoea			From 2 RCTs, a low fat dietary regimens (20-40g fat) / day showed a significant reduction in diarrhoea
bowel activity			From 2 RCTs, a low fat dietary regimens (20-40g fat) / day showed a significant reduction in frequency of bowel motions
Use of medication for diarrhoea			From 2 RCTs, a low fat dietary regimens (20-40g fat) / day showed a significant reduction in diarrhoea rescue medication
COMPARISON IN PATIENTS RECEIVING PELVIC RADIOTHERAPY	LACTOSE MODIFIED DIET	STANDARD CARE	OVERALL RESULT
bowel activity			From 1 RCT, no significant difference between treatments was observed.
COMPARISON IN PCa PATIENTS TREATED WITH RT	REDUCED RESIDUE REGIMEN	OVERALL RESULT	
gastrointestinal symptoms	From a retrospective study, no statistically significant change in gastrointestinal		

	symptoms.		
COMPARISON IN PATIENTS RECEIVING PELVIC RADIOTHERAPY	PROBIOTIC DIET AND MODIFIED FOOD INTAKE	MODIFIED FOOD INTAKE	OVERALL RESULT
bowel activity			From 2 RCTs, probiotic during RT demonstrated a decrease in the mean frequency of bowel movements ($p<0.05$)
Diarrhoea			From 2 RCTs, probiotics during RT demonstrated a decrease in the incidence of diarrhoea ($p<0.01$)
COMPARISON IN PATIENTS RECEIVING PELVIC RADIOTHERAPY	ELEMENTAL SUPPLEMENT DIET	STANDARD CARE	OVERALL RESULT
Diarrhoea			3 studies (1 RCT and 2 observational studies) indicated a statistically significant decrease in the incidence and severity of acute diarrhoeal symptoms
COMPARISON IN PCa PATIENTS TREATED WITH RT	ELEMENTAL SUPPLEMENT DIET	PARENTERAL NUTRITION	OVERALL RESULT
Any improvement with treatment			1 observational study, a significant perceived benefit in the elementally fed intervention group. No objective measures were described.
COMPARISON IN PCa PATIENTS TREATED WITH RT	ELEMENTAL SUPPLEMENT DIET AND MODIFIED	MODIFIED FOOD INTAKE	OVERALL RESULT

	FOOD INTAKE		
bowel activity			1 RCT did not show any significant differences in bowel symptoms.
weight decrement (kg)			1 RCT found no significant differences in weight loss between groups.
COMPARISON IN PCa PATIENTS TREATED WITH RT	PARENTERAL NUTRITION	STANDARD CARE	OVERALL RESULT
Adverse effects			From 2 RCTs, both indicated that the side effects of treatment were improved in the parenteral group.
nutritional improvement			From 2 RCTs, both indicated that nutritional status was improved in the parenteral fed group.
COMPARISON IN PCa PATIENTS TREATED WITH RT	ENZYME SUPPLEMENT	STANDARD CARE	OVERALL RESULT
Diarrhoea	57%	36%	From 1 RCT, In all, 57% of the intervention and 36% of the control group were rated as having moderate or severe bowel symptoms (P=0.11)
COMPARISON IN PCa PATIENTS TREATED WITH RT	PROBIOTIC DIET AND MODIFIED FOOD INTAKE	PLACEBO	OVERALL RESULT
bowel activity			2 RCTs, Neither study identified significant improvements in chronic bowel symptoms in patients

			randomised to the intervention. In one trial, gastrointestinal symptoms improved in both groups. NOTE placebo in 1 trial was not relevant for gastro symptoms.
COMPARISON IN PATIENT WHO HAVE RECEIVED PELVIC RADIOTHERAPY	ELEMENTAL SUPPLEMENT DIET	OVERALL RESULT	
Abdominal distension, malabsorption, pain		Case Report reported complete resolution of symptoms while the patient consumed this diet.	
COMPARISON IN PATIENT WHO HAVE RECEIVED PELVIC RADIOTHERAPY	LOW FAT DIETS	OVERALL RESULT	
bile salt malabsorption		Observation studies: sig. reduction in bile salt malabsorption using a 40g fat-1 day-1 diet in 9 patients was reported. Other study observed only a moderate improvement in symptoms with the use of a bile acid sequestrant in addition to a low-fat diet.	
COMPARISON IN PATIENT WHO HAVE RECEIVED PELVIC RADIOTHERAPY	PARENTERAL NUTRITION	OVERALL RESULT	
radiation enteritis		A cohort study, showed cyclical nocturnal parenteral nutrition was unsuccessful in controlling severe	

		radiation enteritis symptoms in 48% of the patients
weight change (Kg)		A cohort study, showed a mean increase of 12.9 kg
Overall survival		A cohort study reported a 60% survival rate at 1 year with a mean weight gain of 8.7 kg (-2.1 to 15). A retrospective study indicated that cumulative survival in patients supported by home parenteral nutrition was 76% at 1 year.
nutritional improvement		Nutritional status improved in a small cohort
COMPARISON IN PATIENT WHO HAVE RECEIVED PELVIC RADIOTHERAPY	VITAMIN A	OVERALL RESULT
pain		Cohort study; All pain resolved after this intervention.
degree of rectal ulceration		Cohort study; clinical signs of anal ulceration resolved after this intervention.
COMPARISON IN PATIENT WHO HAVE RECEIVED PELVIC RADIOTHERAPY	VITAMIN C AND VITAMIN E	OVERALL RESULT
symptom scores (symptoms = rectal bleeding, rectal pain, quantity of blood, days of diarrhoea, number of stools and urgency)		2 Cohort studies; Stat significant improvements in patient-reported symptoms of bleeding, diarrhoea and urgency, but not pain, were noted and of those patients followed to 1 year, symptom regression was sustained. see

		below for other study results	
symptom scores (symptoms = rectal bleeding, rectal pain, quantity of blood, days of diarrhoea, number of stools and urgency)		The other study reported all symptoms subsiding by 6-12 weeks of treatment	
COMPARISON IN PATIENTS WITH HYPOMAGNESAEMIA AND RADIATION-INDUCED PROCTOSIGMOIDITIS	INTRAVENOUS INFUSION OF MAGNESIUM SULPHATE	LOW-RESIDUE DIET AND USE OF ANTIDIARRHOEAL MEDICATION	OVERALL RESULT
Diarrhoea			Cohort study rapid resolution of diarrhoeal symptoms IV infusion group compared to delayed response on a low-residue diet group

General comments Author's note: Low-fat diets, probiotic supplementation and elemental diet merit further investigation.

Reviewer's Note: This is a well conducted systematic review of studies that have used varied study designs. It provides a diverse evidence base of nutritional interventions; however the study designs provide low quality evidence.

Studies meeting the inclusion criteria but not included in the evidence table

Study	Comments
(Henriksson *et al.* 1991)	Included in Hovdenak et al (2005) meta-analysis
(Kneebone *et al.* 2004)	Included in Hovdenak et al (2005) meta-analysis
(O'Brien *et al.* 1997)	Included in Hovdenak et al (2005) meta-analysis
(Sanguineti *et al.* 2003)	Included in Hovdenak et al (2005) meta-analysis
(Stellamans *et al.* 2002)	Included in Hovdenak et al (2005) meta-analysis
(Valls *et al.* 1999)	Included in Hovdenak et al (2005) meta-analysis

Health Economic Summary

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.

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6 Locally advanced prostate cancer

6.1 In men with prostate cancer, does the addition of adjuvant therapy to radical therapy improve outcomes?

Short Summary

Evidence about neoadjuvant and adjuvant hormonal therapy comes from a systematic review (Kumar *et al.* 2006) of 21 randomised controlled trials.

Neoadjuvant and adjuvant therapy with radical radiotherapy

Several randomised trials (Kumar *et al.* 2006) have shown that adjuvant androgen deprivation 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.

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men who are to have radical therapy for prostate cancer	• neo-adjuvant hormonal therapy • adjuvant hormonal therapy • adjuvant radiotherapy after surgery • neo-adjuvant chemotherapy • adjuvant chemotherapy	Single modality radical treatment	• Overall survival • Disease specific survival • Biochemical disease-free survival • time till salvage hormone intervention • disease recurrence (local, distant metastasis or biochemical i.e. PSA progression) • Pathological staging (which can be expressed in a number of ways either as organ confined rates, pathological over-staging or down-staging compared to clinical staging) • side effects • quality of life • cost

(The search strategy developed from this PICO table and used to search the literature for this question is in Appendix C)

Neoadjuvant hormonal therapy with prostatectomy

Evidence comes from ten randomised trials included in the Kumar and co-workers (Kumar *et al.* 2006) review. See table 6.1.1 for the summary of outcomes. Men treated with neoadjuvant hormonal therapy were significantly more likely to have organ confined disease, and less likely to have positive surgical margins or positive lymph nodes. There was no significant effect of neoadjuvant hormonal therapy on overall or disease free survival.

Kumar and co-workers (Kumar *et al.* 2006) could not pool data about treatment toxicity in their review, for any of the treatment combinations. Data from individual studies suggests a significant increase in adverse events in patients receiving neo-adjuvant

hormonal therapy, with hot flushes being the most common. Two trials (Prezioso *et al.* 2004; Soloway *et al.* 2002) reported a case of myocardial infarction in the hormone treatment group, one of which was fatal. One trial (Klotz *et al.* 2003) reported two cases of pulmonary embolism, one in the standard care group and a fatal case in the hormonal therapy group.

Neoadjuvant hormonal therapy with radiotherapy

Evidence comes from four randomised trials included in the Kumar and co-workers (Kumar *et al.* 2006) review. See table 6.1.4 for summary of outcomes. At five years after radiotherapy, biochemical and clinical disease free survival were significantly better in those who had neoadjuvant hormonal therapy. Five year overall survival was not significantly affected by neoadjuvant hormonal therapy.

Three studies presented data on adverse events. Between 16 and 27% of patients (Lamb *et al.* 2003; Pilepich *et al.* 2001) had to stop the flutamide part of hormonal therapy early, usually due to liver function abnormality or bowel side effects. Patients also experienced transient sexual dysfunction while on maximum androgen blockade. Hot flushes were also a common adverse effect of hormonal therapy (Fellows *et al.* 1992).

Adjuvant hormonal therapy with radiotherapy

Evidence comes from four randomised trials included in the Kumar and co-workers (Kumar *et al.* 2006) review. See table 6.1.5 for summary of outcomes. Adjuvant hormone therapy was associated with improved overall survival at five and ten years after radiotherapy. Adjuvant hormonal therapy was associated with improved disease specific survival at five years after radiotherapy, and improved disease free survival at ten years.

The adjuvant bicalutamide study (Tyrrell *et al.* 2005) suggests that mild to moderate breast pain and gynaecomastia are common side effects of this therapy (seen in 74% and 69% of patients respectively). Withdrawal due to adverse events was 29% in the adjuvant bicalutamide group compared to 10% in the standard care group.

Adjuvant chemotherapy with prostatectomy or radiotherapy

One randomised trial from the pre-PSA era (Schmidt *et al.* 1996), did not observe a survival advantage of adjuvant estramustine or cyclophosphamide over standard care in men with positive lymph nodes after prostatectomy or radiotherapy. A number of small phase I or II trials report the use of adjuvant and neoadjuvant chemotherapy (Macvicar & Hussain 2005). Large phase III trials are underway of neoadjuvant or adjuvant docetaxel or mitoxantrone with prostatectomy (CALGB-90203, SWOG-9921, and RTOG 0521).

1 **Table 6.1.1** Evidence profile for neoadjuvant hormonal therapy with radical prostatectomy
2 **Question:** Should neo-adjuvant hormonal therapy and prostatectomy vs. prostatectomy alone be used for prostate cancer?
3 **Systematic review:** Kumar, Shelley, Harrison, Coles, Wilt and Mason (2006) Cochrane review

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Consistency**	**Directness**	**Other considerations**	**neo-adjuvant hormonal therapy and prostatectomy**	**prostatectomy alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
Overall survival (Follow up: 4 to 7 years)										
3	Randomised trials	No limitations	No important inconsistency	No uncertainty	None	371/407 (91.2%)	386/420 (91.9%)	RR 1.01 (0.67 to 1.85)	7/1 000 (-35 to 36)	□□□□ High
5 year disease free survival[1] (Follow up: 5 years)										
5	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2]	317/569 (55.7%)	287/560 (51.2%)	RR 1.09 (0.97 to 1.20)	45/1 000 (-13 to 105)	□□□□ Moderate
Pathological tumour stage (organ confined) (Follow up: not applicable)										
4	Randomised trials	No limitations	No important inconsistency	No uncertainty	None	215/477 (45.1%)	120/445 (27%)	RR 1.63 (1.40 to 1.86)	200/1 000 (127 to 271)	□□□□

										High
Positive surgical margin status (Follow up: not applicable)										
8	Randomised trials	No limitations	No important inconsistency	No uncertainty	None	193/919 (21%)	384/883 (43.5%)	RR 0.48 (0.4 to 0.56)	227/1 000 (191 to 263)	□□□□ High
Positive lymph nodes (Follow up: not applicable)										
5	Randomised trials	No limitations	No important inconsistency	No uncertainty	None	47/627 (7.5%)	70/620 (11.3%)	RR 0.66 (0.46 to 0.94)	39/1 000 (7 to 61)	□□□□ High

1

Footnotes:

1. No biochemical or clinical progression
2. Meta-analysis does not consider censoring: this underestimates survival probability and could be a source of bias if censoring rates differed between treatment groups.

2

Table 6.1.2. Evidence profile for adjuvant hormonal therapy with radical prostatectomy
Question: Should adjuvant hormonal therapy plus prostatectomy vs. prostatectomy alone be used for prostate cancer?
Systematic review: Kumar, Shelley, Harrison, Coles, Wilt and Mason (2006) Cochrane review

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Consistency**	**Directness**	**Other considerations**	**adjuvant hormonal therapy plus prostatectomy**	**prostatectomy alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
5 year overall survival (Follow up: Median 6.1 to 7.1 years)										
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2]	181/199 (91%)	181/208 (87%)	RR 1.05 (0.97 to 1.09)	39/1 000 (-29 to 80)	□□□□ Moderate
10 year overall survival (Follow up: Median 6.1 to 7.1 years)										
2	Randomised trials	No limitations	Important inconsistency (-1)[1]	No uncertainty	Imprecise or sparse data (-1)[2]	107/199 (53.8%)	134/208 (64.4%)	RR 0.76 (0.58 to 0.92)	155/1 000 (270 to 50)	□□□□ Low
5 year disease free survival (Follow up: Median 6.1 to 7.1 years)										
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-	169/199 (84.9%)	126/208 (60.6%)	RR 1.41 (1.29 to 1.49)	246/1 000 (174 to 297)	□□□□

					1)[2]					Moderate
10 year disease free survival (Follow up: Median 6.1 to 7.1 years)										
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2]	105/199 (52.8%)	77/208 (37%)	RR 1.48 (1.19 to 1.75)	177/1 000 (70 to 279)	□□□□ Moderate

1

Footnotes:

1. Significant heterogeneity: Wirth (2005) shows significantly poorer overall survival with adjuvant hormonal therapy
2. Meta-analysis does not consider censoring: this underestimates survival probability and could be a source of bias if censoring rates differed between treatment groups.

2

Table 6.1.3. Evidence profile for adjuvant radiotherapy with radical prostatectomy
Question: Should adjuvant radiotherapy vs. no adjuvant radiotherapy be used for men having radical prostatectomy for prostate cancer?
Patient or population: men with pathologically advanced prostate cancer
Systematic review: NCCC review

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Consistency	Directness	Other considerations	adjuvant radiotherapy	no adjuvant radiotherapy	Relative (95% CI)	Absolute (95% CI)	
Death from any cause[1,] (Death certificate. Follow up: median 5 to 10.6 years)										
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	None	117/716 (16.3%)	126/714 (17.6%)	RR 0.92 (0.74 to 1.14)	14/1 000 (-25 to 49)	□□□□ High
Biochemical failure (Serial PSA measurements. Follow up: median 5 to 10.6 years)										
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	None	191/674 (28.3%)	332/675 (49.2%)	RR 0.58 (0.5 to 0.67)	206/1 000 (162 to 245)	□□□□ High
Clinical progression (Regular clinical examination and staging studies where clinically indicated. Follow up: median 5 to 10.6 years)										
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	None	159/716 (22.2%)	224/714 (31.4%)	RR 0.71 (0.60 to 0.83)	91/1 000 (53 to 125)	□□□□ High

Death from prostate cancer[2] (Follow up: median 5 years)											
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[3]	8/502 (1.6%)	15/503 (3%)	RR 0.53 (0.23 to 1.25)	14/1 000 (to)	□□□□ Moderate	
Complication rate[3] (Regular clinical examination. Follow up: median 5 to 10.6 years)											
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	None	149/716 (20.8%)	85/714 (11.9%)	RR 1.75 (1.37 to 2.23)	89/1 000 (44 to 146)	□□□□ High	1

1

2

Footnotes:

1. Death from any cause at any time during follow up
2. Not reported how death from prostate cancer was assessed
3. Low event rate
4. Grade 2 or more toxicity (EORTC/RTOG scale) in Bolla (2005); unclear what scale was used in Thompson (2006) trial.

Table 6.1.4. Evidence profile for neoadjuvant hormonal therapy with radical radiotherapy

Question: Should Neo-adjuvant hormonal therapy plus radiotherapy vs. Radiotherapy alone be used for prostate cancer?
Systematic review: Kumar, Shelley, Harrison, Coles, Wilt and Mason (2006) Cochrane review

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Consistency**	**Directness**	**Other considerations**	**Neo-adjuvant hormonal therapy plus radiotherapy**	**Radiotherapy alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
5 year disease specific survival (Follow up: Median 5.9 to 6.7 years.)										
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[3]	353/491 (71.9%)	360/500 (72%)	RR 1.00 (0.91 to 1.07)	2/1 000 (-52 to 61)	□□□□ Moderate
5 year biochemical disease free survival (Follow up: Median 5 to 6.7 years.)										
3	Randomised trials	No limitations	Important inconsistency (-1)[1]	No uncertainty	Imprecise or sparse data (-1)[3]	185/554 (33.4%)	112/543 (20.6%)	RR 1.56 (1.29 to 1.90)	116/1 000 (60 to 186)	□□□□ Low
5 year clinical disease free survival[2] (Follow up: Median 5 to 6.7 years.)										

2	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[3]	148/491 (30.1%)	106/500 (21.2%)	RR 1.46 (1.17 to 1.77)	97/1 000 (37 to 164)	□□□□ Moderate

1

2

Footnotes:

1. Statistically significant heterogeneity in the results.
2. Additional data extraction from original papers was required.
3. Meta-analysis does not consider censoring: this underestimates survival probability and could be a source of bias if censoring rates differed between treatment groups.

Table 6.1.5. Evidence profile for adjuvant hormonal therapy with radical radiotherapy
Question: Should Adjuvant hormonal therapy plus radiotherapy vs. radiotherapy alone be used for prostate cancer?
Systematic review: Kumar, Shelley, Harrison, Coles, Wilt and Mason (2006) Cochrane review

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Consistency**	**Directness**	**Other considerations**	**Adjuvant hormonal therapy plus radiotherapy**	**radiotherapy alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
5 year overall survival (Follow up: Median 5.3 to 14.5 years.)										
4	Randomised trials	No limitations	Important inconsistency (-1)[1]	No uncertainty	Imprecise or sparse data (-1)[3]	1170/1433 (81.6%)	1093/1411 (77.5%)	RR 1.05 (1.01 to 1.09)	41/1 000 (12 to 68)	□□□□ Low
10 year overall survival (Follow up: Median 7.6 to 14.5 years.)										
2	Randomised trials	No limitations	Important inconsistency (-1)[2]	No uncertainty	Imprecise or sparse data (-1)[3]	250/527 (47.4%)	205/532 (38.5%)	RR 1.23 (1.08 to 1.39)	89/1 000 (29 to 150)	□□□□ Low
5 year disease specific survival (Follow up: Median 5.5 to 7.6 years.)										
2	Randomised trials	No limitations	Important inconsistency	No uncertainty	Imprecise or sparse data (-	629/695 (90.5%)	571/697 (81.9%)	RR 1.10 (1.07 to 1.13)	86/1 000 (55 to 110)	□□□□

			(-1)[2]		1)[3]					Low
10 year disease free survival (Follow up: Median 7.6 to 14.5 years.)										
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[3]	199/527 (37.8%)	128/532 (24.1%)	RR 1.59 (1.33 to 1.86)	142/1 000 (80 to 207)	□□□□ Moderate

1

Footnotes:

2

3

1. Significant heterogeneity. Studies with higher baseline risk (Pilepich, 2005; Bolla, 2002) showed more benefit from adjuvant hormonal therapy.
2. Significant heterogeneity

4

5

1 **Evidence Table**

Schmidt, Gibbons, Murphy & Bartolucci. Evaluation of adjuvant estramustine phosphate, cyclophosphamide, and observation only for node-positive patients following radical prostatectomy and definitive irradiation. Investigators of the National Prostate Cancer Project. Prostate 28[1]. 1996.

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: United States

Inclusion criteria Patients with localised. potentially curable, prostate cancer

Exclusion criteria Men with clinical disease stages A and B1 were excluded.

Population -

Interventions Following radical therapy patients were randomised to one of three treatment arms. Adjuvant cyclophosphamide 1 gram/m2-IV every 3 weeks for 2 years, estramustine phosphate 600 mg/m2-po daily for up to 2 years, or to observation only.

Outcomes Clinical recurrence (nearly always defined by a positive bone scan) and disease specific survival.

Follow up Average follow up was 10 years.

Results Only patients with lymph node involvement were included in this analysis.

In a post-hoc subgroup analysis of those with more than 20% lymph node involvement, men treated with estramustine showed significantly better progression free survival than the observation only group.

COMPARISON IN MEN WITH POSITIVE LYMPH NODES AFTER RADIOTHERAPY	ADJUVANT CYCLOPHOSPHAMIDE	ADJUVANT ESTRAMUSTINE	OBSERVATION ONLY	OVERALL RESULT
Clinical progression free survival	45/52 progressed. Median progression free survival was 30.9 months	31/42 progressed. Median progression free survival was 37.3 months	42/52 progressed. Median progression free survival was 20.9 months	no significant difference (p=0.1748, log rank test)
Disease specific survival	25/52 died. Median disease specific survival was 86.7 months	15/42 died. Median disease specific survival was 138.9 months	20/52 died. Median disease specific survival was	no significant difference (p=0.3493, log rank

			93.6 months	test)
COMPARISON IN MEN WITH POSITIVE LYMPH NODES AFTER PROSTATECTOMY	ADJUVANT CYCLOPHOSPHAMIDE	ADJUVANT ESTRAMUSTINE	OBSERVATION ONLY	OVERALL RESULT
Clinical progression free survival	9/16 progressed. Median progression free survival was 51.6 months	13/18 progressed. Median progression free survival was 48.9 months	11/14 progressed. Median progression free survival was 51.7 months	no significant difference (p=0.6984, log rank test)

General comments Pre PSA era study. Treatment toxicity not reported in this paper.

Health Economic Short Summary

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 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.

Health Economic Summary

Overview

All five economic evaluations evaluated the neoadjuvant / adjuvant use of hormonal therapies for people in whom radical treatments were planned. Each study considered a different hormonal regimen. In four evaluations, treatments were 'in addition' to radiotherapy', not surgery. None of the studies was performed from a UK perspective.

The overall quality of the evaluations was considered to be good; each was based on a suitable RCT, and appropriate modelling methods appear to have been used by three of the evaluations. Overall, there appears to be at least reasonable evidence to suggest that the use of hormonal therapies as neoadjuvant / adjuvant treatments are cost-effective (compared to no adjunctive therapy). However, it is not clear which hormonal therapy regimen is the most cost-effective, specifically in terms of treatment duration.

Comparison(s)

In three of the evaluations (Konski, 2006, Neymark, 2001 and Samant 2003), the comparator was radiotherapy alone. In Konski (2005), longterm (2 years) androgen deprivation therapy was compared with androgen therapy that only lasted for the duration of radiotherapy. In the analysis that contained bicalutamide monotherapy (Moeremans, 2004) its addition was compared with 'standard' care, for which relatively few details were provided but it appeared to included radiotherapy, chemotherapy and surgery.

Population Sample

Men with local and / or locally advanced prostate cancer for which radical therapy is planned.

Costs

All 5 evaluations were performed from a health services perspective, although none were from the UK. They considered resources such as the costs of hormonal therapy, radical therapy, adverse events follow-up and biochemical progression. Costs were estimated using a mixture sources, including results from appropriate RCTs and literature reviews (the latter where modelling techniques were employed). No obvious categories of cost were excluded from the analyses that were likely to bias the results in a systematic manner.

Clinical Effectiveness

In each case, clinical effectiveness was estimated using results from appropriate RCTs. For example, Konski et al. 2006 was based on the Radiation and Oncology Group 92-02, where patients with locally advanced prostate cancer were randomised to receive either 2 years androgen deprivation therapy or no further adrogen deprivation therapy following the end of radiotherapy.

Health outcomes were expressed in terms of life-years gained and quality-adjusted life-years (QALYs).

Results

The results ranged from hormonal therapy as an adjunct to radiotherapy 'dominating' radiotherapy alone to costing an additional Euros 27,059 per QALY. No study reported a base case incremental cost-effectiveness ratio above £30,000 per life-year / QALY gained.

Sensitivity Analysis

A number of one- and two-way sensitivity analysis were performed. Broadlly speaking, the results were shown to be sensitive to the time horizon (shorter time horizons were associated with higher incremental cost-effectiveness ratios) and the efficacy of the hormonal therapies. Konski (2006) also reported the results of a probabilistic sensitivity analysis – which suggested there was a 91% probability of long term androgen therapy is cost-effective compared with shorter term adrogen therapy, at the US$50,000 per additional QALY level (although few details of the distributions required to generate this analysis were presented). Similar probablisitic results were also presented in Konski (2005).

Reviewer Comments

All authors concluded that hormonal therapy, within the confines of each individual study, was a cost-effective treatment option.

None of the analysis were performed from a UK NHS prespective, which would have been preferable. However, each analysis was based on a suitable RCT (given each studies objective) – the overall quality of the studies was considered to be good. The analyses did not generally consider the cost-effectiveness of sub-groups, such as those at higher risk of disease progression. Thus there is a possibility that 'average' incremental cost-effectiveness ratios that were reported could contain a degree of heterogeneity, and mask appropriate and inappropriate treatment sub-groups. Additionally, as the studies' evaluated different hormonal regimens, it is not possible to identify which hormonal regimen is the most cost-effective treatment option, particularly in terms of duration of therapy.

Health Economic Evidence Table

Question: What is the cost-effectiveness of different types of neoadjuvant / adjuvant therapies for people in who radical therapy is planned?

Bibliographic reference	Konski, AE. al. Economic analysis of a phase III clinical trial evaluating the addition of total androgen suppression to radiation versus radiation alone for locally advanced prostate cancer (Radiation Therapy Oncology Group protocol 86-10), 2005 International Journal of Radiation Oncology, Biology, Physics 63(3) p. 788-794	Konski, A et al. **Long-term hormone therapy and radiation is cost-effective for patients with locally advanced prostate carcinoma. Cancer, 2006. 106(1). 51-57**	Neymark, NI et al. Cost-effectiveness of the addition of early hormonal therapy in locally advanced prostate cancer: Results decisively determined by the cut-off time-point chosen for the analysis. European Journal of Cancer, 2001. 37(14) p. 1768-1774	Samant, RS. **A cost-outcome analysis of long-term adjuvant goserelin in addition to radiotherapy for locally advanced prostate cancer. Seminars in Urologic Oncology, 2003. 21(3) p. 171-177**	**Moremans K et al. Cost-effectiveness analysis of bicalutamide (Casodex) for the treatment of early prostate cancer. Value in Health, 2004. 7(10) p. 472-481**
Source of funding	Unclear	Unclear	EORTC / AstraZeneca	Northern Cancer Research Foundation	AstraZeneca
Economic study type	Cost-Utility Analysis (CUA)	Cost-Utility Analysis (CUA)	Cost-Effectiveness Analysis (CEA), using life-years gained	CEA, using life-years gained	CUA
Population, country & perspective	Locally advanced, US ($), health	Locally advanced, US ($), health	Locally advanced, France (FF), health	Locally advanced, Canada (CAN$), health	Local and locally advanced, Belgium (Euros), health
Technology	Hormonal therapy (HT) 2 months before and during radiotherapy	Long-Term Androgen-Deprivation (LTAD) and Short-Term Androgen-Deprivation (STAD)	'Early hormonal therapy' as an addition to RT	Adjuvant, starting at the beginning of radiotherapy, for 3-years	Adjuvant bicalutamide monotherapy, in addition to 'standard care', for a maximum of 5-years (standard care is not well

		Both given with RT. Drug treatment started 2 months prior to RT and continuing until RT finished. LTAD, treatment continued for a further 2-years			described)
Comparison(s)	Radiotherapy (RT) alone	LTAD and STAD compared with each other	RT alone	RT alone	'Standard care' (SC) alone, which included the possibility of radiotherapy
Source of effectiveness data	Single RCT with modelling	Single RCT with modelling	Retrospective analysis of single RCT data with modelling	Single RCTand modelling. Effectiveness data analysis on an intention to treat analysis	Single RCT with modelling
Cost components included and health care resource utilization (HCRU)	Included: costs of drug and radiotherapy	Included: Initial cost of of androgen treatment, continued androgen treatment, hormone treatment after biochemical failure and cost of treatment in last year of life	Included: length of hospital stay, clinic visits, surgical operations performed, drugs used for treatment and progression and palliative treatments	Included: costs of drug, radiotherapy, laboratory costs	Included: Costs of adjuvant treatment, follow-up, biochemical progression and metastatic disease
Results – cost per patient per alternative	RT: $29,240; RT+HT: $31,286	LTAD: $32,564; STAD: $33,059	RT: FF71,000; RT+HT: FF58,300;	RT+HT increased costs by an additional $13,200	SC: Euros 9,490; SC+HT: Euros 12,565
Results – effectiveness per patient per alternative	RT: 5.48 QALYs; RT+HT: 6.43 QALYs	LTAD: 4.13 QALYs; STAD: 3.68 QALYs	RT: 5.99 years; RT+HT: 7.05 years	RT+HT increased survival by an additional 1.2 years	SC: 8.95 QALYs; SC+HT: Euros 9.4 QALYs

Incremental cost-effectiveness ratio	$2,153 per additional QALY	LTAD dominates	RT+HT dominates	$16,500 per additional life-year gained (LYG)	Euros 27,059 per additional QALY
Results-uncertainty	Probabilistic analysis undertaken. 86% probability that RT+HT is cost-effective at the $50,000 per additional QALY level	Probabilistic and deterministic sensitivity analysis performed. 91% probability that LTAD was the most cost-effective option at a $50,000 per additional QALY level	Probabilistic sensitivity analysis. Probability of 76% that RT+HT is a less costly and more effective treatment option	Various one and two-way analysis performed.	Various one and two-way analysis performed, including the tim horizon which was shown to particularly alter the results
Time horizon, discount rate	? Benefits ?%; Costs ?%	10 years Benefits 3%; Costs3%	Time horizon ? Benefits ?; Costs3%	10 years Benefits 3%; Costs?	15 years in the base case Benefits 3%; Costs3%
Comments	Good quality analysis. Authors stated that RT+HT the most cost-effective option	Good quality analysis., although few details of the distributions used to conduct the probabistic sensitivity analysis were reported. Authors stated that LTAD is more cost-effective than STAD under all reasonable assumptions	High quality analysis. The authors concluded that RT+HT should be considered the most cost-effective option	Good quality analysis, although more details of the methods used to extrapolate the survival curves would have been useful. The authors concluded that even under pessimistic assumptions, RT+HT is the most cost-effective option	Good quality analysis. The authors concluded that Bicaultaminde monotherapy is the most cost-effective option, although consideration should be given to different subgroups / risks of disease progression

Health Economic Quality Checklist
(Drummond and Jefferson 1996 BMJ 13, 275-283 (August))

Scoring - yes, no, not clear and not appropriate	Study ID	Konski et al. 2005	Konski et al. 2006	Neymark et al 2001.	Samant et al. 2003	**Moremans K et al. 2006**
	Checklist completed by	Alec Miners	Alec Miners	Alec Miners	Alec Miners	Alec Miners
Study design	Was a research question stated?	Yes	Yes	Yes	Yes	Yes
	Was the economic importance of the research question stated?	Yes	Yes	Yes	Yes	Yes
	Was the viewpoint/s of the analysis clearly stated and justified?	Yes	Yes	Yes	Yes	Yes
	Was the rational for choosing the alternative programs or interventions to be compared stated?	Yes	Yes	Yes	Yes	Yes
	Were the alternatives being compared clearly described? (that is, can you tell who? did what? to whom? where? and how often?)?	Yes	Yes	Yes	Yes	'Standard care' only partially described
	Was the form of economic evaluation used, clearly stated?	Yes	Yes	Yes	Yes	Yes
	Is the choice of the economic evaluation justified in relation to the questions addressed?	Yes	Yes	Yes	Yes	Yes
Data	Was the source of the effectiveness	Yes	Yes	Yes	Yes	Yes

collection	estimates used clearly stated?					
	Were the details of the of the design and results of the effectiveness study given? (if based on a single study)	Partially	Yes	Yes	Partially	Partially
	Were the details of the synthesis or meta-analysis of estimates given? (If based on an overview of a number of effectiveness studies)	N/A	N/A	N/A	N/A	N/A
	Was the primary outcome measure/s for the economic evaluation clearly stated?	Yes	Yes	Yes	Yes	Yes
	Were the methods to value health states and other benefits stated?	Partially	Partially	N/A	N/A	Yes partially
	Were the details of the subjects from whom valuations were obtained given?	Partially	Partially	N/A	N/A	Partially
	Were any productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A
	Was the relevance of any productivity changes to the study questions discussed?	N/A	No	N/A	No	No
	Were the quantities of resources reported separately from their unit costs?	Yes	No	Yes	Partially	Yes
	Were the methods for estimation of quantities and unit costs described?	Yes	Yes	Yes	Yes	Yes
	Was the currency and price data	Yes	Price year was	Yes	Yes	Yes

	recorded?		unclear			
	Were the details of currency of price adjustments for inflation or currency conversion given?	No	Unclear	No	No	No
Modelling	Were the details of any model used given?	Yes	Partially, no schematic provided	Yes	No	Yes
	Was the choice of model and the key parameters on which it was based justified?	Yes mostly	Partially	Yes mostly	No	Partially
Analysis and interpretation of results	Was the time horizon of costs and benefits stated?	Unclear	Yes	Unclear	Yes	Yes
	Was the discount rate stated?	Unclear	Yes	Yes	Yes for benefits	Yes
	Was the choice of discount rate justified?	N/A	No	Yes	No	No
	Was an explanations given if costs or benefits were not discounted?	N/A	N/A	No	No	N/A
	Were the details of statistical tests and confidence rates given for stochastic data?	N/A	N/A	Partially	N/A	N/A
	Was the approach to sensitivity analysis given?	Yes	Yes	Partially	Yes	Partially
	Was the choice of variables for sensitivity analysis justified?	Yes	Yes	Partially	Partially	Partially
	Were the ranges over which the	Partially, few details of	Partially, few details of	Partially	No	Yes

	variables are varied stated?	distribution parameters were given	distribution parameters were given			
	Were relevant alternatives compared?	Yes	Yes	Yes	No	Partially
	Was the incremental analysis reported?	Yes	Yes	Yes	Yes	Yes
	Were the major outcomes presented in a disaggregated as well as aggregated form?	Yes	Yes	Yes	No	Yes
	Was the answer to the study question given?	Yes	Yes	Yes	Yes	Yes
	Did the conclusions follow from the data reported?	Yes	Yes	Partially	Yes	Yes
	Were the conclusions accompanied by the appropriate caveats?	Yes	Yes	Yes mostly	Yes	Yes
This and the following have been retained from Appendix G	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (for example, distribution of costs and consequences, or relevant ethical issues)?	Yes partially	Yes partially	Partially	Partially	Yes, partially
	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	No	No	Partially	Yes partially	No

OVERALL ASSESSMENT OF THE STUDY	How well was the study conducted? *Code ++, + or –*	+	+	++	+	+
	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes	Yes	Yes	Yes	Yes

1

2

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7 Metastatic prostate cancer

7.1 In men with metastatic prostate cancer, which type of initial hormone therapy is the most clinically effective?

Short Summary

Intermittent androgen deprivation

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

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
▪ Men with metastatic disease usually defined on bone scan or CT scan or any other site; ▪ Men with locally advanced disease usually defined on DRE; ▪ Men with biochemical failure after previous radical treatment defined on serial PSA assays; ▪ Men who have nodal involvement	▪ Medical castration ▪ Continuous hormonal therapy	▪ surgical castration ▪ Intermittent hormonal therapy ▪ maximal androgen blockade ▪ Monotherapy with anti-androgens	▪ Overall Survival ▪ Disease specific survival ▪ Symptom control ▪ Side effects (Including adverse psychosocial sequelae) ▪ QALY ▪ cost

(The search strategy developed from this PICO table and used to search the literature for this question is in Appendix C)

Evidence Summary

Intermittent versus continuous androgen deprivation therapy (IAD versus CAD)

Literature searches identified a systematic review of five randomised trials (Conti *et al.* 2007) and a review and meta-analysis of non-randomised studies (Shaw *et al.* 2007). The systematic review also listed four ongoing randomised trials of intermittent androgen deprivation which have yet to report.

Overall Survival
None of the trials in the systematic review analysed overall or disease specific survival. Shaw and co-workers (Shaw *et al.* 2007) reported a meta-analysis of individual patient data to identify risk factors for mortality in men treated with IAD for localised or metastatic prostate cancer. On multivariate analysis, duration of treatment, type of medication (MAB or not), restart PSA threshold, initial PSA value and PSA nadir were all significant predictors of overall survival. Results were incompletely reported and it is unclear the degree to which each variable predicted survival.

Disease specific survival

In one of the randomised trials included in the systematic review (de Leval *et al.* 2002) with a median follow up of 2.4 years, 12.1% of men treated with CAD had died of prostate cancer compared with 5.7% of men treated with IAD. Disease specific survival was not a primary endpoint in this trial, however and was not analysed statistically.

Side effects

Data about adverse effects could not be pooled in the systematic review (Conti *et al.* 2007), because of clinical and methodological differences between the studies. The general finding was that adverse event rates were lower in the IAD than the CAD groups, but not to a statistically significant degree. The small sample size in the trials limited the power of such comparisons. Two of the trials reported significantly lower rates of impotence in the IAS groups; but one trial did not find a significant difference. The reviewers concluded that IAD may have slightly reduced adverse effects. Sexual potency was similar in IAD and CAD groups, although IAD was superior during the off-treatment interval.

Symptom control and quality of life

There was no evidence from randomised trials about these outcomes.

Evidence tables

Systematic reviews of RCTs

Collette, Studer, Schroder, Denis & Sylvester . Why phase III trials of maximal androgen blockade versus castration in M-1 prostate cancer rarely show statistically significant differences. Prostate 48[1]. 2001.

Design: Systematic review of RCTs (therapy), evidence level: 1+

Inclusion criteria The prostate cancer trialists' meta-analysis (2000) is re-analysed. The original analysis included randomised trials comparing MAB with castration alone, for men with prostate cancer.

Exclusion criteria -

Population -

Interventions Maximum androgen blockade (LHRH agonist plus antiandrogen) versus LHRH alone. Short term antiandrogen at the start of LHRH-only treatment (to prevent tumour flare) was not given in some trials: these were excluded for the meta-analysis.

Outcomes Overall mortality

Results -

COMPARISON IN MEN WITH ADVANCED PROSTATE CANCER	LHRH AGONIST PLUS ANTIANDROGEN	LHRH AGONIST PLUS PLACEBO	OVERALL RESULT
Overall survival	not reported	not reported	No significant difference, HR=0.95 [95% C.I. 0.89 to 1.02]

General comments The paper also includes an analysis of statistical power over time, suggesting that trials were often underpowered (reporting survival outcomes too soon).

(Conti *et al.* 2007)
Design: Systematic review of RCTs (therapy), evidence level: 1+ Country: , setting: Tertiary care **Inclusion criteria** Randomised or quasi-randomised trials comparing intermittent and continuous androgen deprivation, in men with prostate cancer. **Exclusion criteria** Prior androgen deprivation therapy. **Population** number of patients = 1382. **Interventions** Intermittent and continuous androgen deprivation (IAS and CAS). The review protocol specified an initial treatment period of 6 months **Outcomes** Primary outcome was overall mortality. Secondary outcomes: disease specific mortality, duration of response to treatment, testosterone levels, quality of life (measured using recognised scales), side effects and treatment drop-out or loss to follow-up rate. **Follow up** Reviewers note that follow-up was generally short. **Results** Five studies, with 1382 patients, were included. All included men with advanced prostate cancer (T3 or T4). Androgen deprivation was: cyproterone acetate only (1 trial), chlormadinone acetate + LHRHa (1 trial), nilutamide + buserelin (1 trial) and flutamide + goserelin (1 trial) The review authors state that the clinical and methodological diversity in the trials meant that the results could be pooled in a meta-analysis. No studies analysed survival or metastatic progression One study (De Leval, 2002) reported no difference between biochemical progression in the IAS and CAS groups. Trials reported adverse events. The general finding was that adverse events were reduced in the IAS groups, but not to a statistically significant degree. The small sample size of most of the trials limits the power of such comparisons. Two of the trials reported significantly lower rates of impotence in the IAS groups, one trial did not find a significant difference. Reviewers conclude that IAS may have slightly reduced adverse effects. Sexual potency was similar in IAS and CAS groups, although IAS was superior during the off-treatment interval.

1 Randomized controlled trials

Iversen, Tyrrell, Kaisary, Anderson, van, Tammela, Chamberlain, Carroll & Melezinek . Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of follow-up. J Urol 164[5]. 2000.

Design: Randomized controlled trial (therapy), evidence level: 1

Country: , setting: Tertiary care

Inclusion criteria Men with PSA more than 20 ng/ml and T3-T4, M0 prostate cancer, recruited to one of two randomised trials. (Men with M1 disease were analysed in another publication).

Exclusion criteria Previous systemic therapy for prostate cancer, radiotherapy in the previous 3 months, other invasive malignancy in the last five years and ECOG performance score of 3 or 4.

Population number of patients = 480.

Interventions Men were randomised to receive either bicalutamide (150 mg per day) or castration orchiectomy or goserelin acetate 3.6 mg every 28 days).

Outcomes Overall survival, and objective disease progression. Quality of life was assessed using self administered questionnaires. The treating physicians recorded adverse events.

Follow up Median follow up was 6.3 years.

Results Overall mortality was 56%, and disease progression was 77%.

COMPARISON IN MEN WITH LOCALLY ADVANCED PROSTATE CANCER	BICALUTAMIDE MONOTHERAPY	CASTRATION	OVERALL RESULT
Overall survival	Median survival was 63.5 months	Median survival was 69.9 months	No sig. difference, HR for mortality 1.05 [95%C.I. 0.81 to 1.36]
Disease progression	Not reported separately (median 2.7 years from graph)	Not reported separately (median 2.8 years from graph)	No sig. difference, HR for mortality 1.20 [95%C.I. 0.96 to 1.51]
Withdrawals due to adverse drug reactions	4.1%	not reported	
Gynaecomastia	49.4%	4.4%	

Breast pain	40.1%	1.9%
Hot flushes	13.1%	50%

1

Usami M, Akaza H, Hirano Y, Kagawa S, Kanetake H, Naito S, Sumiyoshi Y, Takimoto Y, Terai A, Yoshida H & Ohashi Y . Bicalutamide 80 mg combined with a luteinizing hormone-releasing hormone agonist (LHRH-A) versus LHRH-A monotherapy in advanced prostate cancer: findings from a phase III randomized, double-blind, multicenter trial in Japanese patients. Prostate Cancer Prostatic Dis . 2007.

Design: Randomized controlled trial (therapy), evidence level: 1

Country: Japan, setting: Tertiary care

Inclusion criteria Age 20 years or more, histologically proven advanced (stage C or D) prostate cancer, measurable lesions, baseline PSA 10 ng/ml or more and life expectancy of at least 3 months.

Exclusion criteria Thresholds were set for liver enzymes, serum creatinine, white blood cell count, haemoglobin, and platelets. Other active malignancy, dyspnoea hypersensitivity to LHRH agonist, or refractory cardiac failure.

Population number of patients = 205.

Interventions Men were randomised to receive either bicalutamide 80 mg or placebo daily. In addition, all men had an LHRH agonist: goserelin acetate 3.6 mg or leuprorelin acetate 3.75 mg (at the choice of the investigator) given by injection every four weeks.

Bicalutamide was withdrawn in the event of disease progression. Patients with disease progression in either arm were treated at the investigators discretion.

Outcomes PSA normalisation (PSA 4 ng/ml or less), tumour response (at least partial response according to Criteria for Efficacy Evaluation of Non-Invasive Treatment of Prostate Cancer), overall survival, withdrawal due to adverse events.

Follow up Men were assessed at 1,4,5,8 and 12 weeks after starting treatment, and then every 4 weeks until either disease progression or treatment withdrawal. 132/203 patients discontinued treatment, due largely to disease progression (72 cases) or adverse events (36 cases).

Results -

COMPARISON IN MEN WITH ADVANCED PROSTATE CANCER	LHRH-A PLUS BICALUTAMIDE	LHRH-A MONOTHERAPY	OVERALL RESULT
PSA normalisation	96/102	59/101	Favours MAB, HR 3.96 [95% CI 2.77 to

			5.66], p<0.001
Treatment failure	54/102	78/101	Favours MAB, HR 0.54 [95% CI 0.38 to 0.77], p<0.001
Disease progression	30/102	57/101	Favours MAB, HR 0.40 [95% CI 0.26 to 0.63], p<0.001
Overall mortality	13/102	18/101	Not analysed
Withdrawals due to adverse drug reactions	9/102 (8.8%)	11/101 (10.9%)	96% CI on difference -10.7% to 6.4%

General comments -

1

Akaza . Superior anti-tumor efficacy of bicalutamide 80 mg in combination with a luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist monotherapy as first-line treatment for advanced prostate cancer: Interim results of a randomized study in Japan. Jpn. J Clin Oncol 34[1]. 2004.

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: Japan

Inclusion criteria Age 20 years or more, histologically proven advanced (stage C or D) prostate cancer, measurable lesions, baseline PSA 10 ng/ml or more and life expectancy of at least 3 months.

Exclusion criteria Thresholds were set for liver enzymes, serum creatinine, white blood cell count, haemoglobin, and platelets. Other active malignancy, dyspnoea hypersensitivity to LHRH agonist, or refractory cardiac failure.

Population number of patients = 205.

Interventions Men were randomised to receive either bicalutamide 80 mg or placebo daily. In addition, all men had an LHRH agonist: goserelin acetate 3.6 mg or leuprorelin acetate 3.75 mg (at the choice of the investigator) given by injection every four weeks.

Bicalutamide was withdrawn in the event of disease progression. Patients with disease progression in either arm were treated at the investigators discretion.

Outcomes PSA normalisation (PSA 4 ng/ml or less), tumour response (at least partial response according to Criteria for Efficacy Evaluation of Non-Invasive Treatment of Prostate Cancer), withdrawal due to adverse events.

Follow up Men were assessed at 1,4,5,8 and 12 weeks after starting treatment. 79/205 patients discontinued treatment, due largely to disease progression (43 cases) or adverse

events (23 cases).

Results -

COMPARISON IN MEN WITH ADVANCED PROSTATE CANCER	LHRH AGONIST PLUS BICALUTAMIDE	LHRH AGONIST PLUS PLACEBO	OVERALL RESULT
Three month PSA normalisation rate	81/102 (79.4%)	39/101 (36.6%)	Favours MAB (p<0.001), estimated difference 40.8% [95% C.I. 27.6% to 52%]
Three month tumour response rate	79/102 (77.5%)	66/101 (65.3%)	No sig. difference (p=0.063)
Withdrawals due to adverse drug reactions	9/102 (8.8%)	11/101 (10.9%)	(p not reported). Estimated difference -2.1% [95% C.I. -10.7% to 6.4%]

General comments -

1

de, Boca, Yousef, Nicolas, Jeukenne, Seidel, Bouffioux, Coppens, Bonnet, Andrianne & Wlatregny . Intermittent versus continuous total androgen blockade in the treatment of patients with advanced hormone-naive prostate cancer: results of a prospective randomized multicenter trial. Clinical Prostate Cancer 1[3]. 2002.

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: Belgium

Inclusion criteria Men less than 80 years of age with advanced prostate cancer (T3-T4 disease and/or metastatic disease). Men with disease recurrence after curative treatment were also included if their PSA was at least 4 ng/ml.

Exclusion criteria Untreated clinically localised disease, other malignancy, psychiatric or senile disorders, prior hormonal or chemotherapy, or severe associated illness.

Population number of patients = 77.

Interventions All men were initially treated with flutamide (3 times 250 mg daily) for 15 days to avoid tumour flare. Men were then treated with maximum androgen blockade (flutamide plus goserelin acetate) for a minimum of 3 months and a maximum of 6 months. Men whose PSA normalised (successive decreasing values less than 4 ng/ml) were then randomised to either intermittent androgen deprivation (IAD) or continuous androgen deprivation (CAD).

Men in the IAD arm discontinued androgen blockade after the induction cycle and restarted it if their PSA rose to above 10 ng/ml. Medication was stopped again if their PSA normalised (using the above definition).

Outcomes Hormone refractory progression free survival. Adverse event rates

Follow up 68/77 patients were randomised to either IAD or CAD. Median follow-up was 36.4 months, range 10.2 to 29.7 months.

Results 4 men in the CAD group died of hormone refractory prostate cancer compared with 2 in the IAD group.

COMPARISON IN MEN WITH ADVANCED PROSTATE CANCER	INTERMITTENT ANDROGEN DEPRIVATION	CONTINUOUS ANDROGEN DEPRIVATION	OVERALL RESULT
3 year disease progression rate	7.0% [S.E. 4.8%)	38.9% (S.E. 11.2%)	Favours IAD, log rank test (p=0.0052)
Withdrawals due to adverse drug reactions	1/35	2/33	Not analysed statistically

General comments Small trial

Systematic review of cohort studies

Shaw, Wilson, Cuzick, Prowse, Goldenberg, Spry & Oliver . International study into the use of intermittent hormone therapy in the treatment of carcinoma of the prostate: a meta-analysis of 1446 patients. BJU Int . 2007.

Design: Systematic review of cohort studies (therapy), evidence level: 2-

Inclusion criteria Published papers using the keywords "intermittent hormone/androgen ablation" in phase II trials in men with prostate cancer. Study reference lists were also checked. Only papers whose authors agreed to contribute individual patient data were included.

Exclusion criteria -

Population number of patients = 1446.

Interventions Phase II trials of intermittent androgen deprivation (IAD). No comparison groups of continuous androgen deprivation were included.

Outcomes Overall survival, duration of remission.

Follow up The meta-analysis covered the 4 years after the start of hormone treatment.

Results 366/1466 had confirmed nodal or distant metastases at the start of treatment. Of the other 1080 patients with no apparent metastases: 517 had IAD as primary therapy and 563 had IAD for recurrent disease after radical therapy.

Prognostic factors for overall survival

On Cox proportional hazards analysis, duration of treatment, type of medication (MAB or not), restart PSA threshold, initial PSA value and PSA nadir were all significant predictors of overall survival. Results, however, were incompletely reported and it is unclear the degree to which each variable predicted survival.

General comments -

Retrospective comparative study

Rosendahl, Kiebert, Curran, Cole, Weeks, Denis & Hall . Quality-adjusted survival (Q-TWiST) analysis of EORTC trial 30853: comparing goserelin acetate and flutamide with bilateral orchiectomy in patients with metastatic prostate cancer. European Organization for Research and Treatment of Cancer. Prostate 38[2]. 1999.

Design: Retrospective comparative study (therapy), evidence level: 3

Inclusion criteria The paper is a secondary analysis of an RCT in men with advanced prostate cancer.

Exclusion criteria -

Population number of patients = 327.

Interventions Survival and toxicity data were taken from an EORTC trial in which men were randomised to receive either MAB (goserelin acetate plus flutamide or orchiectomy.

Utility values associated with various health states were taken from another cross sectional study of men with prostate cancer

Outcomes Quality adjusted survival (using the Q-TWisT method). The quality of life (QOL) health states in the study were: time with hot flushes due to treatment, time without progression of disease and treatment side effects, and time with progression of disease.

Follow up Health states were analysed over the 7 years after initiation of treatment. For 30/327 patients no follow-up data were available and these men were excluded from the analysis.

Results Analysis suggested 5.2 quality adjusted months in favour of MAB [95% C.I. -1.1-11.5], due mainly to the differences in overall survival in this trial

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General comments -

Review

Klotz, Schellhammer & Carroll . A re-assessment of the role of combined androgen blockade for advanced prostate cancer. BJU Int 93[9]. 2004.
Design: Review (therapy), evidence level: 3 **Interventions** This paper reports an indirect comparison of bicalutamide plus castration versus castration alone, using data from the prostate cancer trialists meta-analysis and a MAB trial comparing flutamide and bicalutamide (Schellhammer et al. Br J Urol 1997; 80: 278) **Outcomes** Overall survival. **Results** The hazard ratio of mortality (MAB with bicalutamide vs. castration) was 0.80 [95% C.I. 0.66 to 0.98], suggesting an absolute survival benefit of between 2 and 34% for MAB with bicalutamide. **General comments** This method requires prognostic risk factors to be similar in the Schelhammer and PCTG patient groups. The authors acknowledge that it is unclear whether this is the case.

Studies meeting the inclusion criteria but not included in the evidence table

Study	Comments
Samson, Seidenfeld, Schmitt, Hasselblad, Albertsen, Bennett, Wilt & Aronson . Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer 95[2]. 2002.	Repeat publication of Seidenfeld review (2001) - MAB vs. monotherapy
Seidenfeld, Samson, Hasselblad, Aronson, Albertsen, Bennett & Wilt . Single-therapy androgen suppression in men with advanced prostate cancer: A systematic review and meta-analysis. Ann Intern.Med 132[7]. 2000.	Publication of part of Seidenfeld (2001) review, comparison of monotherapies

Health Economic Short Summary

The literature review identified 183 potentially relevant economic evaluations. Ten papers were obtained, but only 2 were considered to be full economic evaluations and reviewed in full. One of these papers was published in Japanese, but an English summary was available.

Bayoumi et al (2000) conducted the first evaluation in 2000, as part of a US Agency for Health Care Research (AHRQ) research project. The evaluation represents an extremely comprehensive evaluation that compared 6 different treatment strategies for the first-line choice of hormone treatment for advanced prostate cancer: 1) diethylstilbestrol [DES] 2) bilateral orchiedctomy 3) non steroidal antiandrogen [NSAA] 4) LHRH monotherapy 5) NSAA in combination with a LHRH and 6) NSAA and bilateral orchidectomy. The economic evaluation was underpinned by a systematic review of appropriate randomised controlled trials and a meta-analysis. A Markov model was also constructed, which took into account the progression of the patients underlying prostate cancer and the side effects due to individual treatments. The framework used for the analysis was a cost-utility analysis from a health services perspective. A cost-effectiveness analysis, using survival as the outcome measure, was also conducted.

The results showed that it cost an extra £6100 and £7500 per additional life-year and QALY gained, respectively, if orchidectomy was used instead of DES. All other treatment options, including LHRH monotherapy, were dominated by orchidectomy (ie. they were more costly and less effective). These results were robust to most alternative assumptions, except when different utility values were assumed. This finding is important, as the analysis did not take into account patients' preferences for different courses of action. For example, for surgical or medical castration. Nonetheless, the authors concluded that orchiectomy was the most cost-effective treatment option.

The second evaluation, by Fujikawa et al. (2003) was published in Japanese, but an English summary was available for review. The evaluation was similar Bayoumi et al. in so much that it was based on a review of the literature, meta-analysis and Markov modelling exercise. It also compared a number of different options as first-line hormone therapies for advanced prostate cancer: 1) DES 2) orchidectomy 3) orchidectomy and NSAA 4) LHRH monotherapy and 5) LHRH monotherapy and NSAA. However, an important difference between the two evaluations is that Fujikawa et al (2003) attempted to allow for individual preferences (for medical versus surgical castration) by multiplying the health state utilities of orchidectomy by 0.94 – although a justification for this value is not provided. Thus health outcomes associated with orchidectomy were considered to be of 'less value' compared to purely medical alternatives. The overall quality of the evaluation was judged to be good.

The baseline results from the analysis showed that compared to orchidectomy, LHRH monotherapy cost approximately £17,500 per additional QALY gained. However, it is unclear what the incremental cost-effectiveness ratio would have been if the 0.94 weighting had been removed. It is also unclear whether future health benefits were discounted (in Bayoumi et al (2000) they were discounted at 3% per annum). Indeed, minimal sensitivity analysis means that it is difficult to assess the robustness of the results to alternative assumptions.

Health Economic Evidence Tables

Question: Initial hormone therapy for advanced disease?

By: Alec Miners

Date: 26/09/07

1

Bibliographic reference	Bayoumi, AM et al. Cost-effectiveness of androgen suppression therapies in advanced prostate cancer. 2000, Journal of the National Cancer Institute. 92 (21) p. 1731-1739 And: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.section.5381	Fujikawa,K et al. Cost-utility analysis of androgen ablation therapy in metastatic prostate cancer. 2003, Japanese Journal of Urology. 94 (4) p. 503-512. Printed in Japanese but English summary available
Source of funding	Supported by the Blue Cross and Blue Shield Association Technology Evaluation Centre. Developed under contract with the Agency for Healthcare Research and Quality	None stated
Economic study type	Cost-Effectiveness Analysis (CEA – in terms of life-years gained) Cost-Utility Analysis (CUA)	Cost-Utility Analysis (CUA)
Population, country & perspective	Metastatic prostate cancer(65 year old men), US ($), health (and societal?)	Symptomatic metastatic prostate cancer (65 year old men), Japanese Yen, health
Technology	6 strategies were compared as first line therapy: 1) diethylstilbestrol [DES] 2) bilateral orchiectomy 3) non steroidal antiandrogen [NSAA] 4) LHRH monotherapy 5) NSAA in combination with a LHRH 6) NSAA and bilateral orchiectomy	5 therapies were compared as first-line therapy: 1) diethylstilbestrol diphosphate [DES] 2) orchiectomy 3) orchiectomy and nonsteroidal antiandrogen [NSAA] 4) LHRH monotherapy 5) LHRH monotherapy and NSAA.
Comparison(s)	-	-
Source of effectiveness data	Meta-analysis of RCTs combined with Markov modelling	Review of RCTs combined with Markov modelling
Cost components included and health care resource utilization (HCRU)	Included: costs of all medicines, second line therapies, orchiectomy, side-effects, preterminal care and health state specific results (for the following health states: local recurrence, asymptomatic disease and symptomatic disease)	Included: The costs of hormone therapy, side effects, hospitalisations and orchiectomy. Non-prostate related costs were excluded from the analysis.
Results – cost per patient per alternative	In US$ 1) $3600 2)$7000 3)$16100 4) $27000 5) $40300 and 6) $20700 [discounted results]	1) Y103,572 2) Y289,049 3) Y727,516 4) Y858,312 and 5) Y1,187,227
Results – effectiveness	Life-Years Gained:	QALYs:

per patient per alternative	1) 5.96 2) 6.52 3) 6.38 4) 6.50 5) 6.48 and 6) 6.49 QALYs: 1) 4.64 2) 5.10 3) 4.98 4) 5.08 5) 5.03 and 6) 5.05	1) 2.51 2) 2.54 3) 2.56 4) 2.68 and 5) 2.64
Incremental cost-effectiveness ratio	$6100 per additional Life-Years Gained from using orchiectomy alone compared with DES. All other strategies were dominated by orchiectomy alone. $7500 per additional QALY Gained from using orchiectomy alone compared with DES. All other strategies were dominated by orchiectomy alone.	Relative to DES: Y5,522,888/QALY for orchiectomy, Y12,499.713/QALY for orchiectomy plus NSAA, Y4,288,295/QALY for LHRH, and Y8,168,254/QALY for LHRH plus NSAA Incremental analysis: LHRH plus NSAA was excluded as it was dominate whereas orchiectomy plus NSAA was excluded due to extended dominance Orchiectomy compared with LHRH monotherapy Y4,066,164 (approximately £17,500)
Results-uncertainty	Deterministic one- and two-way sensitivity analysis. Results particularly dependent on the utility weights associated with health states and side-effects	One-way sensitivity analysis. Few reported but the authors stated that the effect of maximum androgen blockade treatment has to be more than 12% higher than that of single treatment methods (ie. orchiectomy and LHRH).
Time horizon, discount rate	Life-time (approximately 4.5 years) Benefits 3%; Costs 3%	10 year time horizon Benefits ?%; Costs 3%
Comments	High quality analysis. Authors concluded that bilateral orchiectomy was the most cost-effective treatment option. But they acknowledged / implied that the analysis did not take into account patient levels of acceptability (ie preferences) regarding the different treatment options.	Reasonable quality analysis (only a summary available in English). Authors concluded that LHRH monotherapy was a cost-effective use of resources compared with orchiectomy. An attempt was made to adjust for patient preferences (for medical therapy) by multiplying utilities by 0.94 in the baseline results. However, it

		is unclear how this 0.94 was derived.

Health Economic Quality Checklist
(Drummond and Jefferson 1996 BMJ 13, 275-283 (August))

Scoring - yes, no, not clear and not appropriate	Study ID	Jager et al. 2000	Fujikawa et al. 2003
	Checklist completed by	Alec Miners	Alec Miners
Study design	Was a research question stated?	Yes	Yes
	Was the economic importance of the research question stated?	Yes	Yes
	Was the viewpoint/s of the analysis clearly stated and justified?	Yes	Yes
	Was the rational for choosing the alternative programs or interventions to be compared stated?	Yes	Yes
	Were the alternatives being compared clearly described? (that is, can you tell who? did what? to whom? where? and how often?)?	Yes	Yes, mostly
	Was the form of economic evaluation used, clearly stated?	Yes	Yes
	Is the choice of the economic evaluation justified in relation to the questions addressed?	Yes	Yes
Data collection	Was the source of the effectiveness estimates used clearly stated?	Yes	Yes
	Were the details of the of the design and results of the effectiveness study given? (if based on a single study)	N/A	Yes
	Were the details of the synthesis or meta-analysis of estimates given? (If based on an overview of a number of effectiveness studies)	Yes	Yes, mostly
	Was the primary outcome measure/s for the economic evaluation clearly stated?	Yes	Yes
	Were the methods to value health states and other benefits stated?	Partially	Partially

	Were the details of the subjects from whom valuations were obtained given?	Partially	Partially
	Were any productivity changes (if included) reported separately?	Unclear. Societal perspective stated but costs other than for health care are not quoted in the text	N/A
	Was the relevance of any productivity changes to the study questions discussed?	?	N/A
	Were the quantities of resources reported separately from their unit costs?	Partially	Partially
	Were the methods for estimation of quantities and unit costs described?	Partially	Partially
	Was the currency and price data recorded?	Yes	Yes
	Were the details of currency of price adjustments for inflation or currency conversion given?	Yes	No
Modelling	Were the details of any model used given?	Yes	Yes
	Was the choice of model and the key parameters on which it was based justified?	Yes mostly	Yes
Analysis and interpretation of results	Was the time horizon of costs and benefits stated?	Yes	Yes
	Was the discount rate stated?	Yes	Yes, for costs
	Was the choice of discount rate justified?	No	No
	Was an explanations given if costs or benefits were not discounted?	N/A	N/A
	Were the details of statistical tests and confidence rates given for stochastic data?	N/A	N/A
	Was the approach to sensitivity analysis given?	Yes	Partially
	Was the choice of variables for sensitivity analysis justified?	Partially	Partially
	Were the ranges over which the variables are varied stated?	Partially	No
	Were relevant alternatives compared?	Yes	Yes
	Was the incremental analysis reported?	Yes	Yes

	Were the major outcomes presented in a disaggregated as well as aggregated form?	Partially	Partially
	Was the answer to the study question given?	Yes	Yes
	Did the conclusions follow from the data reported?	Yes	Yes
	Were the conclusions accompanied by the appropriate caveats?	Yes	Yes
This and the following have been retained from Appendix G	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (for example, distribution of costs and consequences, or relevant ethical issues)?	Yes	Yes
	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	Yes	Partially
OVERALL ASSESSMENT OF THE STUDY	How well was the study conducted? *Code ++, + or –*	++	+
	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes	Yes

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7.2 In men who have been treated with hormonal therapy for prostate cancer, what are the effective interventions for managing the complications of hormone therapy?

Short Summary

Hot flushes
Placebo controlled randomised trials have demonstrated that megestrol acetate, diethylstilbestrol and progestogens are effective in the treatment of hot flushes in men receiving hormonal therapy. Very small randomised trials have shown beneficial results from the use of oestrogen patches and cyproterone acetate. A small case series suggested that intramuscular medroxyprogesterone acetate reduced the frequency and severity of hot flushes.

Gynaecomastia
A systematic review by Di Lorenzo and co-workers (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 antiandrogens. A narrative review of the evidence supported the effectiveness of both radiotherapy and tamoxifen, although there were theoretical concerns that, as an antioestrogen, tamoxifen could reduce the effectiveness of hormonal therapy.

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men treated with hormonal therapy for prostate cancer	Interventions for hormonal therapy related: • hot flushes • gynaecomastia • sexual dysfunction • lethargy • bone demineralisation • cardiac dysfunction • cognitive dysfunction. • fractures	No intervention comparators	• Quality of life • Reduction in symptoms

(The search strategy developed from this PICO table and used to search the literature for this question is in Appendix C)

Volume of Evidence

Prevention of hot flushes
Loprinzi (Loprinzi *et al.* 1994a) examined the effect of clonidine on the median daily frequency and severity of hot flushes in men with hot flushes after medical or surgical castration for prostate cancer. There was no significant difference between clonidine and placebo arms in terms of frequency or severity of hot flushes but clonidine was associated with increased dry mouth and redness under the patch.

Oestrogens
Atala and co-workers (Atala *et al.* 1992) examined the effect of diethylstilbestrol on the frequency and severity of hot flushes in men experiencing hot flushes following bilateral orchiectomy for prostate cancer. DES reduced the mean daily number of hot flushes

compared with placebo (DES 0.35 vs. placebo 6.92). Complete resolution of hot flushes was seen in 86% of the men diethylstilbestrol group compared with 0% in the placebo group. Full analysis and data were not presented. The investigators stated that treatment with diethylstilbestrol was associated with gynaecomastia and breast tenderness, but they did not report the rates.

Gerber and co-workers (Gerber *et al.* 2000) compared the effect of low dose (0.05mg) and high dose (0.10mg) estradiol patches on the frequency, severity and duration of hot flushes in 12 men treated with medical castration for advanced prostate cancer. A significant reduction in both frequency (baseline 6.9 vs. 4.4; p=0.02) and severity (baseline 6.5 vs. 4.5; p=0.02) of hot flushes was seen with high dose estradiol compared with baseline over the 12 week study, whereas only a significant reduction in the severity (6.5 baseline vs. 4.8 ;p=0.02)of hot flushes was seen with low dose estradiol. A moderate or major improvement was seen in 25% of the low dose estradiol group compared with 67% of the high dose group.

Antiandrogens
A randomised placebo-controlled cross-over trial by Eaton and McGuire (Eaton & McGuire 1983) examined the effect of cyproterone acetate (100mg three times daily) on the frequency and severity of hot flushes in 12 men with hot flushes after orchiectomy for prostate cancer. There was a statistically significant reduction in the incidence of hot flushes with cyproterone acetate after 3 weeks treatment. The mean number of hot flushes per day was around two for men during the treatment period compared with around 10 during the placebo period. Five of the 12 men complained of lethargy, severe enough to reduce dosage in one case.

Progestogens
A second study by Loprinzi (Loprinzi *et al.* 1994b) examined the effect of megestrol acetate 20mg BD on the daily frequency and severity of hot flushes in 66 men who had undergone surgical or medical orchiectomy who had bothersome hot flushes for at least a week. A significant reduction in both frequency (megestrol acetate group 20% of baseline versus placebo 81% of baseline; p<0.001 in favour of MA) and severity (p<0.001 in favour of MA). 79% of men in the megestrol acetate group and 12% in the placebo group reported at least 50% reduction in daily frequency of hot flushes (p<0.001 in favour of MA).

Langenstroer and co-workers (Langenstroer *et al.* 2005) reported a series of 48 men treated with intramuscular medroxyprogesterone acetate (either 400mg or 150mg) At both dosages the treatment significantly reduced the frequency and severity of hot flushes, although the higher dose appeared more effective. The authors reported no treatment related side effects.

Prevention of gynaecomastia and breast pain
A systematic review by Di Lorenzo and co-workers (Di Lorenzo *et al.* 2005) considered interventions for prevention and treatment of gynaecomastia and breast pain associated with antiandrogens. A narrative review of the evidence supported the effectiveness of both radiotherapy and tamoxifen, but the authors concluded tamoxifen was the more effective of the two options.

A randomised trial by Perdona and co-workers (Perdona *et al.* 2005) examined the effect of tamoxifen (10mg BD) and radiotherapy (12Gy single dose) in 151 men with confirmed

prostate cancer who had undergone prostatectomy and were being treated with bicalutamide. Over a treatment period of 12 months tamoxifen significantly reduced the development of gynaecomastia compared with no tamoxifen (OR 0.1; 95% CI 0.8-0.12; p=0.009) and breast pain (OR 0.1; 95% CI 0.7-0.11; p=0.009. Similarly radiotherapy significantly reduced the development of gynaecomastia compared with no radiotherapy (OR 0.51 95% CI 0.47-0.5; p=0.008) and breast pain (OR 0.43; 95% CI 0.40-0.45) but to a lesser extent than tamoxifen.

Boccardo and co-workers (Boccardo *et al.* 2005) examined the effect of tamoxifen 20mg or anastrozole 1mg in 114 men with localised or advanced prostate cancer taking bicalutamide. Over a treatment period of 48 weeks tamoxifen significantly reduced percentage of patients who developed gynaecomastia (no tamoxifen 73% vs. tamoxifen 10% vs. anastrozole 51%; p<0.001 in favour of tamoxifen) and breast pain (no tamoxifen 39% vs. tamoxifen 6% vs. anastrozole 27%; p=0.01 in favour of tamoxifen). Adverse events were reported in 38%, 35% and 70% of patients respectively, and serious adverse events were reported in 10%, 11% and 14% respectively.

Other outcomes

Segal and co-workers (Segal *et al.* 2003) examined the effect of a 12 week resistance exercise programme on 82 men with prostate cancer scheduled to receive androgen therapy. Resistance exercise reduced fatigue and improved quality of life (p<0.01).

Evidence table

Systematic reviews of RCTs

Di Lorenzo, Autorino, Perdona and De Placido. Management of gynaecomastia in patients with prostate cancer: a systematic review. [Review] [11 refs]. The Lancet [6] Dec 2005 972-979

Design: Systematic review of RCTs (therapy), evidence level 1-

Country:

Setting: Secondary care

Inclusion criteria No formal inclusion criteria. English language papers by use of keywords “gynaecomastia”, “prostate cancer”, “radiation therapy”, “hormonal therapy” and “mastectomy”. Abstracts were also assessed.

Exclusion criteria None stated.

Population Patients with prostate cancer. Patients in included trials were treated for prostate cancer with a variety of methods/drugs (diethylstilbestrol or leuprorelin or bicalutamide or oestrogen or tetrasodium testestrol or polyestradiol or flutamide or finasteride or orchiectomy or LHRH analogues)

Interventions

Treatment:

Radiotherapy 10Gy to 33.3Gy vs. no radiotherapy/sham radiotherapy/tamoxifen [7 references];

Tamoxifen 10mg to 30mg/day [2 references]

Prevention:

Radiotherapy 6Gy to 40 Gy vs. no radiotherapy [4 references];

Tamoxifen vs. anastrozole/placebo/no tamoxifen [4 references]

Outcomes

Number of patients who developed gynaecomastia

Breast pain

Follow up – Unknown up to 1 year

Results

TREATMENT WITH RADIOTHERAPY			
	Radiotherapy (12-15Gy) single fraction	No radiotherapy (n=79)	OVERALL RESULT

Number of patients % who developed gynaecomastia	(n=174) 48 (27%)	 56 (71%)	 p<0.001 at 1 year
Number of patients % who developed gynaecomastia	Radiotherapy (10Gy as single dose) (n=52) 27 (52%)	Sham radiotherapy (n=54) 46 (85%)	OVERALL RESULT OR 0.13, 95% CI 0.04-0.38 at 1 year reduction in breast pain (p=0.0429)
Number of patients % who developed gynaecomastia	Radiotherapy (12Gy) single fraction (n=18) 10 (56%)	Tamoxifen 10mg (n=17) 2 (12%)	OVERALL RESULT not reported
Number of patients % who developed gynaecomastia	Radiotherapy (8-15Gy) (n=262) 29 (11%)	No comparator	OVERALL RESULT NA
Number of patients % who developed gynaecomastia	Radiotherapy (<12Gy) (n=5) / Radiotherapy (12Gy) (n=43) / Radiotherapy (15Gy) (n=39) 10 (11%) mild 11 (13%) moderate 1 (1%) severe		OVERALL RESULT NA
Number of patients % who developed gynaecomastia	Radiotherapy (33.3Gy) single fraction (n=27) 3 (11%)	No radiotherapy (n=20) 17 (85%)	OVERALL RESULT not reported
PREVENTION WITH RADIOTHERAPY			
	Radiotherapy (two 6 Gy fractions) (n=51)	No comparator	OVERALL RESULT

Number of patients % who developed gynaecomastia	Improved in 7 (26%) and resolved in 2 (7%) at 3 months – of 27 patients who had gynaecomastia			NA
Number of patients % who developed gynaecomastia	Radiotherapy (12Gy as a single dose) (n=50) 17 (34%)	No radiotherapy (n=51) 35 (69%)		OVERALL RESULT not reported
Number of patients % who developed gynaecomastia	Radiotherapy (20-40Gy after hormonal treatment) (n=11) >50% reduction in 3 (27%)	No comparator		OVERALL RESULT NA
Number of patients % who developed gynaecomastia	Radiotherapy (23.75Gy) (n=16) 17 (68%)	Radiotherapy (14.25Gy) (n=9)		OVERALL RESULT not reported
TREATMENT WITH HORMONES				
Number of patients % who developed gynaecomastia	Tamoxifen 10-30mg /day for 1 month (n=6) Gynaecomastia reduction	No comparator		OVERALL RESULT NA
Number of patients % who developed gynaecomastia	Tamoxifen 10mg BD (n=1) Resolved in 1 month	Tamoxifen 10mg BD (n=1) Improved in 1 month	Tamoxifen 10mg OD for 3 months Improved in 6 weeks	OVERALL RESULT
PREVENTION WITH HORMONES				
	Placebo (n=40)	20mg tamoxifen/day for 48 weeks (n=37)	1mg anastrozole/day for 48 weeks (n=35)	OVERALL RESULT

Number of patients % who developed gynaecomastia	29 (73%)	4 (10%)	18 (51%)	Significant difference between tamoxifen (p<0.001) compared with placebo or anastrozole (Also p<0.001 for breast pain) Significant difference between anastrozole and placebo
Number of patients % who developed gynaecomastia	No tamoxifen (n=51) 35 (69%)	10mg tamoxifen OD for 24 weeks (n=50) 4 (8%)		OVERALL RESULT Significant difference between groups in development of gynaecomastia (p<0.025) and breast pain (p<0.05)
Number of patients % who developed gynaecomastia or breast pain	20mg tamoxifen OD for 3 months (n=35) 4 (11%)	1mg anastrozole OD for 3 months (n=36) 23 (64%)	Placebo for 3 months (n = 36) 25 (69%)	OVERALL RESULT Significant difference between tamoxifen and placebo. NS between anastrozole and placebo
Number of patients % who developed gynaecomastia	tamoxifen 20mg/week (n=30) Significant reduction of gynaecomastia and breast pain	No tamoxifen (n=30)		OVERALL RESULT not reported

General comments –

Methods unclear, time points not always stated, baseline characteristics not provided, no inclusion or exclusion criteria. Studies with small sample size included (n=3!); studies without

control groups included, dosing schedules varied, gynaecomastia assessed using a number of different methods including breast ultrasonography, calliper, or direct questioning of patients. No analysis of results.

Authors conclude that tamoxifen or radiotherapy or both prevent or reduce gynaecomastia or breast pain associated with antiandrogen use, but that tamoxifen is more effective.

Randomised controlled trials

Perdona, S; Autorino R; De, Placido S; D'Armieno, M. Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial. Lancet Oncology, 2005, 6 (5), pp295-300.

Design: Randomised controlled trial (therapy), evidence level 1- (unblinded)

Country: Italy

Setting: Secondary care

Inclusion criteria Men who had histologically confirmed prostate cancer, no distant metastases, and no evidence of current gynaecomastia or breast pain. All patients had undergone radical prostatectomy.

Exclusion criteria Previous hormonal treatment for prostate cancer; metastatic disease; evidence of biochemical relapse after primary treatment; haematological (haemoglobin $\leq$100 g/l, white cell count <3x10^9 cells/l, and platelet count <100x10^9 cell/l), renal (creatinine $\geq$115 mmol/l), or hepatic (transaminases and bilirubin concentrations $\geq$50% normal value) dysfunction; or any comorbidity that could contraindicate use of trial drugs.

Population Number of patients = 151 randomised from January 2002 to February 2004.

Patients were stratified according to primary treatment; disease stage; node involvement; Gleason score and PSA.

Interventions 51 patients randomised to 150mg bicalutamide (BC) only for 24 weeks; 50 patients to 150mg bicalutamide/day and 10mg tamoxifen (TX)/day for 24 weeks; 50 patients to 150mg bicalutamide per day for 24 weeks plus 12 Gy radiotherapy (RT) (directed to 5cm diameter of tissue centred around each nipple) given in one dose on the same day of starting bicalutamide.

Patients assigned bicalutamide alone who subsequently developed gynaecomastia or moderate-severe breast pain that was higher than grade 3 were randomly allocated to 150mg bicalutamide per day and 10 mg tamoxifen per day for 24 weeks or to 150mg bicalutamide per day and 12 Gy radiotherapy given in one fraction on the day of starting bicalutamide.

Outcomes

Primary outcome: frequency of gynaecomastia or breast pain assessed monthly. Gynaecomastia measured with callipers (grade 1-4 with 4 being the largest i.e. >6cm diameter). Breast pain (none, mild, moderate, severe) assessed by patient questioning.

Secondary outcomes: safety; tolerability; relapse-free survival as assessed by PSA concentration; quality of

life assessed every 3 months (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 – 100 point scale with high score representing high level of functioning)

Follow up Gynaecomastia and breast pain monthly to 12 months

Questionnaires – 0, 3, 6 and 9 and 12 months

Results Tamoxifen and radiotherapy both significantly reduced the frequency of gynaecomastia; however, tamoxifen was superior to radiotherapy.

OUTCOME OF INTEREST	Group A BC (150mg OD) alone (n=51)	Group B BC (150mg OD) and TX (10mg OD) (n=50)	Group C BC (150mg OD) and RT (single 12Gy dose) (n=50)	Group D BC (150mg OD) alone followed by TX (10mg for 24 weeks) when gynaecomastia or breast pain developed (n = 17)	Group E BC (150mg OD) alone followed by RT (single 12Gy dose) when gynaecomastia or breast pain developed (n = 18)	OVERALL RESULT
Number % of patients who developed grade 3-4 gynaecomastia	35 (69%)	4 (8%)	17 (34%)	2 (12%)	10 (56%)	Group A vs. Group B OR 0.1 [95% CI 0.8-0.12], p=0.0009 in favour of group B Group A vs. Group C OR 0.51 [95% CI 0.47-0.54], p=0.008 in favour of group C Group D vs. Group A OR 0.2 [0.18-0.22], p=0.02 in favour of group D
Breast pain	29 (57%)	3 (6%)	15 (30%)	6 and 9 month data - 4/14 (29%)	6 and 9 month data - 12/15 (80%)	Group A vs. Group B OR 0.1 [95% CI 0.7-0.11], p=0.009 in favour of group B Group A vs. Group C OR 0.43 [95% CI 0.40-0.45], p=0.02 in favour of group C Group D vs. Group E OR 0.35 [95% CI 0.33-0.38, p=0.045] in favour of group D

General comments – All RT associated adverse events resolved and were of short duration (median 4 weeks). Patients assigned BC and RT had more asthenia than other groups (NS), whereas those in BC and TX group had more constipation, diarrhoea and pruritis (NS). Quality of life scores were not significantly different between tamoxifen and radiotherapy groups at baseline, 3, 6, 9 or 12 months. Relapse-free survival was not significantly different between groups. An improvement in erectile dysfunction scores (IIEF-5 – higher score) at 6 and 12 months was seen in Groups A, B and C (p=NS between groups).

Study was unblinded. Assessment of pain was arbitrarily scored according to severity.

Authors conclude tamoxifen and radiotherapy prevented gynaecomastia and breast pain in some patients receiving bicalutamide monotherapy, and that tamoxifen was more effective than radiotherapy in prevention and treatment of gynaecomastia and breast pain. Quality of life and sexual function were not negatively influenced by RT or Tamoxifen.

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Boccardo, F; Rubagotti A; Battaglia, M. Evaluation of tamoxifen and anastrozole in the prevention of gynaecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. Journal of Clinical Oncology, 2005 23 (94), pp.808-815

Design: Randomised controlled trial (therapy), evidence level 1-

Country: Italy

Setting: Secondary care

Inclusion criteria Patients with localized or locally advanced prostate cancer who were unsuitable for or refused radical prostatectomy or definitive radiotherapy or patients with recurrent disease after primary therapy; histologically confirmed prostate cancer, >50% increase in PSA nadir values after prior radical prostatectomy or radiotherapy that was confirmed by two subsequent determinations 4 week apart (biochemical recurrence), and a wish to avoid the effects of androgen deprivation.

Exclusion criteria Metastatic disease at diagnosis or clinically detectable recurrent disease after ≤10g/dl, WBC count ≤3000, and platelet count ≤90,000/ul), renal (creatinine ≥2.2 ng/nl), or liver (transaminases and bilirubin levels ≥50% of normal levels) dysfunction; and any comorbid condition that could contraindicate the use of one or more of the trial drugs or could jeopardize patient compliance.

Population Number of patients = 114 randomised from December 2000 to February 2002.

14 ineligible patients (4 in BC and BC-TX group and 6 in BC-AZ group) remained in the analyses. 7 patients (5 in BC-TX group and 1 each in BC and BC-AZ group) were evaluated separately has they already had gynaecomastia at time of first breast ultrasonography.

Interventions 40 were assigned to bicalutamide 150mg alone (BC group); 37 were assigned to bicalutamide 150mg plus tamoxifen 20mg (BC-TX group); 36 were assigned to bicalutamide 150mg plus anastrozole 1mg (BC-AZ group).

All patients received three tablets orally once a day to maintain blinding.

Outcomes

Primary outcome: frequency of gynaecomastia or breast pain assessed every 3 months. Gynaecomastia measured with callipers or ultrasound (graded 1-4 with 4 being the largest). Breast pain (none, mild, moderate,

severe) assessed by patient questioning.

Secondary outcomes: safety; tolerability; relapse-free survival as assessed by PSA concentration; quality of life assessed every 3 months using 30-item questionnaire (questionnaire not specified)

Follow up

Gynaecomastia and breast pain 0, 3, 6, 9 months and 48 weeks

Questionnaires – 0, 3, 6 and 9 and 48 weeks

Results Tamoxifen significantly reduced bicalutamide-induced gynaecomastia and breast pain. Anastrozole was not as effective as tamoxifen.

OUTCOME OF INTEREST	Group A BC 150mg/day alone	Group B BC 150mg/day and TX 20mg/day	Group C BC 150mg/day and AZ1mg/day	OVERALL RESULT
Number % of patients who developed grade 3-4 gynaecomastia (all patients n=103)	73%	10%	51%	Group A vs. Group B p<0.001 in favour of tamoxifen Group B vs. Group C p<0.001 in favour of tamoxifen Group A vs. Group C p=NS
Number % of patients who developed grade 3-4 gynaecomastia (patients assessed through ultrasound n=70)	92%	14%	70%	Group A vs. Group B p<0.001 in favour of tamoxifen Group B vs. Group C p<0.001 in favour of tamoxifen Group A vs. Group C p=0.04 in favour of anastrozole

Number % of patients who developed grade 3-4 gynaecomastia (patients assessed through breast calliper n=33)	33%	14%	17%	Group A vs. Group B p =0.05 in favour of tamoxifen Group B vs. Group C p = NS Group A vs. Group C p=NS
Breast pain	39%	6%	27%	Group A vs. Group B p= 0.01 in favour of tamoxifen
Number of patients % with adverse events Number of patients % with serious adverse events	15 (37.5%) 10%	13 (35.1%) 11%	25 (69.5%) 14%	Group A vs. Group C p=0.01 in favour of bicalutamide only Group B vs. Group C p=0.007 in favour of tamoxifen

General comments – Study suggests that incidence and severity of gynaecomastia may be related to the assessment method used (bicalutamide 150mg alone seemed to induce gynaecomastia in 33% of patients monitored using callipers compared with 92% of those monitored using breast ultrasound p<0.001)

Addition of tamoxifen or anastrozole to bicalutamide had no detrimental effect on QOL (data not presented).

Authors conclude anastrozole did not significantly reduce the incidence of bicalutamide-induced gynaecomastia and breast pain. In contrast, tamoxifen was effective, without increasing adverse events.

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Loprinzi CL; Goldber, RM. Transdermal clonidine for ameliorating post-orchiectomy hot flashes. Journal of Urology, 1994, vol. 151 (93), pp. 634-636

Design: Randomised crossover trial (therapy), evidence level 1+ (borderline 1-)

Country: US

Setting: Secondary care

Inclusion criteria Men with a history of prostate cancer who had undergone a medical or surgical orchiectomy and were suffering from hot flashes. Hot flashes had to be present for more than 1 month with a frequency of at least 7 times per week. Patients were required to have a life expectancy of at least 6 months and have an Eastern Cooperative Oncology Group performance status of at least 0 or 1.

Exclusion criteria Concurrent or planned therapy with antineoplastic chemotherapy, androgens, estrogens, progestational agents, corticosteroids, monoamine oxidase inhibitors, levodopa, piribedil, tricyclic antidepressants or sedatives, such as benzodiazepines or barbiturates. Poorly controlled hypertension, coronary insufficiency, a history of myocardial infarction, symptomatic coronary artery disease, peripheral

vascular or cerebrovascular disease, syncope, symptomatic hypotension, significant hepatic or renal dysfunction, a history of significant mental depression, widespread skin disease that would preclude the use of skin patches for medication delivery, or a history of allergic or adverse reactions to clonidine.

Population Number of patients = 77 randomised between September 1990 and April 1992

Patients were stratified according to type of orchiectomy (surgical versus medical obtained with gonadotropin-releasing hormone agonist), duration of hot flash symptoms, average frequency of hot flashes and interval since orchiectomy.

Interventions

Patients were assigned to receive either 4 weeks of transdermal clonidine (0.1mg equivalent daily dose) followed by 4 weeks of placebo patches or vice-versa. Patches were changed weekly.

Outcomes

Frequency and severity (mild, moderate, severe or very severe graded 1 to 4) of hot flashes -assessed through use of patient-completed daily questionnaire

Adverse events

Follow up

Baseline, 4 weeks and 8 weeks

Results Clonidine did not significantly decrease hot flash frequency or severity in patients with post-orchiectomy hot flashes.

OUTCOME OF INTEREST	Group A Clonidine first (n=38)	Group B Placebo first (n = 39)	OVERALL RESULT
Median frequency of hot flashes (baseline week)	8.4	7.1	p=0.72 between groups
Median severity of hot flashes (baseline week)	1.7	1.9	p=0.23 between groups

General comments – Full efficacy data not presented. Analyses during treatment periods failed to demonstrate any significant difference between clonidine and placebo. Clonidine therapy was associated with increased dry mouth (p=0.03) and redness under the patch (p=0.03). At end of treatment period 47% patients “couldn’t tell whether either treatment was better”, 34% chose clonidine and 19% chose placebo (p=0.13).

Authors conclude clonidine failed to reduce incidence or severity of hot flashes resulting from medical or surgical orchiectomy.

Segal EJ; Reid RD; Courneya KS et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. Journal of clinical oncology [21] 9, 2003; 1653-1659
Design: Randomised controlled trial (therapy), evidence level 1+ Country: Canada Setting: Community **Inclusion criteria** Patients with histologically documented prostate cancer, were scheduled to receive androgen deprivation therapy for at least 3 months after recruitment, and if the treating oncologist provided consent. **Exclusion criteria** Severe cardiac disease (New York Heart Association class III or greater), uncontrolled hypertension (blood pressure >160/95 mm/Hg), uncontrolled pain, unstable bone lesions, or residence more than 1 hour from the study centre. **Population** Number of patients = 155 randomised from September 1999 to August 2001. Patients stratified according to centre and intent of treatment (curative i.e. those receiving androgen deprivation therapy in neoadjuvant and adjuvant settings or palliative i.e. those with metastatic disease) **Interventions** Intervention group (n=82) - personalised resistance exercise programme.12 week programme of nine strength-training exercise carried out under supervision three times a week. Exercises included leg extension, calf raises, leg curl, chest press, latissimus pull down, overhead press, triceps extension, biceps curl, and modified curl ups. Patients were instructed to increase resistance once they were able to complete 12 repetitions. Control group (n=73) – men were offered identical exercise advice and guidance; however it was not provided until after the 12 week waiting period. **Outcomes** Primary outcomes: fatigue (13-item Functional assessment of cancer therapy – fatigue: max score 52 – higher score indicates less interference from fatigue on activities and roles in daily living; change score greater than 0 represents a reduction in fatigue, whereas negative score indicates greater fatigue) and health-related quality of life (Functional Assessment of Cancer Therapy – Prostate (FACT – P) scale: Secondary outcomes: muscular fitness (standard load test) and body composition (body weight, BMI, waist circumference, subcutaneous skin folds) **Follow up** Baseline and 12 weeks. During intervention period, 8 men (9.8%) dropped out in the intervention group compared with 12 men (16.4%) in the control group (p=NS). **Results** Resistance exercise reduces fatigue and improves quality of life and muscular fitness in men with prostate cancer receiving androgen deprivation therapy.

OUTCOME OF INTEREST	Group A Resistance Exercise (n=82)	Group B No resistance exercise (n=73)	OVERALL RESULT
Change in fatigue score (baseline to 12 weeks)	+0.8 points	-2.2 points	Group A vs. Group B p=0.002 in favour of resistance exercise
Health-related quality of life	+2.0 points	-3.3 points	Group A vs. Group B p=0.001 in favour of resistance exercise
Upper body muscular fitness (chest press repetitions)	+13.1	-2.6	Group A vs. Group B p =0.009 in favour of resistance exercise
Lower body muscular fitness (leg press repetitions)	+11.8	-1.6	Group A vs. Group B p< 0.001 in favour of resistance exercise

Atala, Admin and Harty. Diethylstilbestrol (DES) in treatment of post-orchidectomy vasomotor symptoms and its relationship with serum follicle-stimulating hormone, luteinizing hormone, and testosterone. Urology 39 [2] 108-110 1992

Design: Randomised crossover trial (therapy), evidence level 1-

Country: US

setting: Secondary care

Inclusion criteria No formal inclusion criteria. Patients who underwent bilateral orchiectomy for prostatic carcinoma at centre during five year period (1983 to 1988).

Four patients took DES before orchiectomy.

Exclusion criteria None stated. No additional hormonal therapy after orchiectomy.

Population Number of patients = 14

(26 initially underwent post-orchidectomy; only those experiencing hot flushes were randomised to DES or placebo n = 14).

Interventions Patients were randomised to Diethylstilbestrol (DES 1mg per day) or placebo for 12 weeks.

Outcomes

Attack and duration of flushing recorded by patient on diary card with severity of attacks rated as mild, moderate or severe; Mean daily number of hot flushes reported in table; side effects;

blood pressure; pulse rate; serum FSH, LH and testosterone levels.

Follow up – Patients were seen at five predetermined times throughout the trial (no specific time points reported)

Results

OUTCOME OF INTEREST	Diethylstilbestrol	Placebo	OVERALL RESULT
Mean daily number of hot flushes	0.35 (AS calculation)	6.92 (AS calculation)	not reported
Complete resolution of hot flushes	12/14 (86%)	0%	not reported
Significant reduction in frequency, duration and severity of hot flushes	2/14 (14%)	not reported	not reported
Moderate reduction in frequency, duration and severity of hot flushes	not reported	3/14 (21%)	not reported
Adverse effects	Gynecomastia and breast tenderness		not reported

	(no figures reported)

General comments –

Methods unclear, time points not stated, baseline characteristics not provided, no formal inclusion or exclusion criteria. No analysis of results.

Authors conclude that the treatment of post-orchidectomy symptoms can be effectively and inexpensively managed with a low dose of DES.

General comments – Of 507 eligible patients only 155 (30.6%) agreed to participate. Attendance at resistance exercise sessions averaged 79% (28 of 36 sessions). Resistance exercise improved symptoms of fatigue, health-related quality of life and muscular fitness of men regardless of whether they were treated with curative or palliative intent or if androgen therapy had been received for less than 1 year or $\geq$ 1 year. No difference between groups for changes in body composition. It was noted that anaemia should have been measured as this may be a possible explanation for the difference observed.

Authors conclude that resistance exercise improved symptoms of fatigue and health-related quality of life in men with prostate cancer receiving androgen deprivation therapy.

Eaton and McGuire. Cyproterone acetate in treatment of post-orchiectomy hot flushes. Lancet December 10th, 1983

Design: Randomised crossover trial (therapy), evidence level 1-

Country: UK

Setting: Secondary care

Inclusion criteria No formal inclusion criteria. Patients with troublesome post-orchidectomy hot flushes

Exclusion criteria None stated

Population Number of patients = 12 (mean age 67.4 years, range 63.5-72.5)

First three weeks of study 8 patients received cyproterone acetate and 4 received placebo

Interventions Patients were randomised to cyproterone acetate (100mg three times daily) or placebo for 3 weeks.

1 week washout between treatments followed by crossover for 3 weeks.

Outcomes Mean daily number of flushes over 21 day period recorded on diary charts (individual patient data only)

Side effects

Follow up Patients reviewed in clinic at end of each phase of treatment (3 weeks)

Results

OUTCOME OF INTEREST	Cyproterone acetate	Placebo	OVERALL RESULT
Mean daily number of hot flushes	individual patient results only	individual patient results only	p<0.001 'reduction in incidence of hot flushes with cyproterone acetate'. Does not specify whether this is vs. baseline or placebo.
Adverse effects	Lassitude in 5/12		

General comments –

Methods unclear, baseline characteristics not provided, no inclusion or exclusion criteria. No analysis of results.

Authors conclude that cyproterone acetate was effective in reducing frequency of hot flushes.

Gerber, Zagaja, Ray & Rukstalis . Transdermal estrogen in the treatment of hot flushes in men with prostate cancer. Urology 55[1]. 2000.

Design: Randomised crossover trial (therapy), evidence level 1-

Country: US

Setting: Secondary care/home

Inclusion criteria Inclusion criteria not formally stated. Advanced prostate cancer (stage C or D or a rising prostate-specific antigen level after radical prostatectomy or radiation therapy) who were receiving leuprolide injections every 1 or 3 months. All patients had been receiving leuprolide injections for at least 1 year at the time of study entry. Each man was experiencing moderate to severe hot flushes, as defined by a minimum daily occurrence of three episodes that the patient found to be bothersome for at least 3 months.

Exclusion criteria Receiving estrogenic medications or had history of deep venous thrombosis, significant coronary artery diseases, or cerebrovascular disease.

Population Number of patients = 12

Interventions Patients were randomised to receive either low dose (0.05mg) or high dose (0.10mg) estrogen patch twice weekly for 4 weeks followed by a 4 week washout period. The final 4 weeks patients either received high dose or low dose patches depending on the initial randomisation. Patients were instructed to apply the patch twice weekly to dry, hairless skin.

Outcomes

Mean number of hot flushes daily

Mean severity of hot flushes based on visual analogue scale

Mean duration of hot flushes

Subjective rating of change in hot flushes

Side effects (including asked specifically about whether they had developed pain, swelling, or tenderness of the breast tissue)

Follow up

Treatment response assessed by daily logs and questionnaires completed every 4 weeks at end of weeks 1,5,9 and 13 of study period.

Results

OUTCOME OF INTEREST	Low dose estrogen patch (0.05mg)	High dose estrogen patch (0.10mg)	OVERALL RESULT
Mean number of hot flushes daily	baseline 6.9 vs. 5.3 (p = 0.09)	baseline 6.9 vs. 4.4 (p=0.02)	Significant reduction with high dose (0.10mg) estrogen only
Mean severity of hot flushes based on visual analogue scale where 1 is least severe and 10 is most severe	baseline 6.5 vs. 4.8 (p=0.02)	baseline 6.5 vs. 4.5 (p=0.02)	Significant reduction with both low dose and high dose estrogen patches

Mean duration of hot flushes	Not reported	Not reported	No change with either high dose or low dose
Moderate or major improvement in symptoms	3/12 (25%)	8/12 (67%)	In favour of high dose estrogen (p=0.04)
Adverse effects	Painless breast swelling 1/12 (8%)	Painless breast swelling 4/12 (33%)	

General comments –

Text and table III do not agree – have taken data from table.

Small study.

Subjective patient measurement.

Authors conclude that transdermal estrogen appears to be a promising, well-tolerated therapy for men with hot flushes after endocrine treatment

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Loprinzi, Michalak, Quella, O'Fallon, Hatfield, Nelimark, Dose, Fischer, Johnson, Klatt, Bate, Rospond, Oesterling. Megastrol Acetate for the prevention of hot flashes. NEMJ 331[6] 347-352 1994

Design: Randomised crossover trial (therapy), evidence level 1-

Country: US

Setting: Secondary care

Inclusion criteria Women with a history of breast cancer (n = 97) or men who had undergone a surgical bilateral orchiectomy or a so-called medical orchiectomy with the use of gonadotrophin-releasing-hormone agonist (n=66). Bothersome hot flashes for at least one month (defined as hot flashes that occurred at least seven times per week and were sufficiently severe that the patient desired therapeutic intervention). Life expectancy of six months or more

Tamoxifen (20mg per day) was permitted

Exclusion criteria Current or planned therapy with antineoplastic chemotherapy, androgens, estrogens, progestational agents, or corticosteroids. Women who were breast-feeding and those with child bearing potential.

Population Number of patients = 166 (100 women and 66 men) recruited from May 1992 to May 1993 (1 woman withdrew before starting medication and 2 women were ineligible).

All patients stratified according to duration of hot flashes and average daily frequency of hot flashes. Men were stratified according to type of orchiectomy and duration of androgen ablation.

Interventions After one week pre-treatment observation period, the patients received megestrol acetate (Megace) 20mg twice daily for 4 weeks followed by placebo for four weeks, or vice versa as determined by randomisation. Medication administered as two coded, blister-packed medication cards. Instructed to take on table twice each day

Outcomes

Mean number of hot flashes daily (adjusted by dividing this number by average number of hot flashes per day at baseline).

Mean daily hot-flash score during last week of given treatment period (adding total number of mild hot flashes plus twice the number of moderate hot flashes plus three times the number of severe hot flashes plus four times the number of very severe hot flashes recorded in a given week and then dividing the sum by the number of days on which values were recorded)

Patient preference at end of study.

Selected toxic effects (appetite changes, fluid retention)

All outcomes patient-rated in diary/questionnaires

Follow up Patients evaluated every two weeks at medical centre or contacted by telephone..

Results

OUTCOME OF INTEREST	Megestrol acetate (20 mg twice daily)	Placebo	OVERALL RESULT
% of baseline daily average number of hot flashes (men)	20%	81%	In favour of megestrol acetate p<0.001
Median hot flash score (men)	13	84	In favour of megestrol acetate p<0.001
% male patients reporting 50% reduction in daily frequency of hot flashes during first treatment period (ITT analysis)	26/33 (79%)	4/33 (12%)	In favour of megestrol acetate p<0.001

General comments – NB Allocated 1- as analysis protocol changed post-study. Would be allocated 1+ if parallel trial. Only results for men presented in table by reviewer (AS). Same trial as Quella 1998.

Crossover analyses had to be ignored because of significantly different carryover effects, reflecting a persistent reduction in hot flashes during the placebo period in the patients who received megestrol acetate first. Only results for the first 4 weeks were therefore used.

91% of men provided efficacy data.

No difference in effect between patients according to sex, age, baseline severity of hot flashes duration of hot flashes or use of tamoxifen.

Authors conclude low dose megestrol acetate is well tolerated and can substantially decrease the frequency of hot flashes in men.

Quella, Loprinzi, Sloan, Vaught, DeKrey, Fischer, Finck, Pierson, Pisansky. Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes.1998

Design: Telephone interview following randomised crossover trial (Loprinzi), evidence level 3

Country: US

Setting: Home

Inclusion criteria Women with a history of breast cancer or men who had undergone a surgical bilateral orchiectomy or a so-called medical orchiectomy with the use of gonadotrophin-releasing-hormone agonist. Bothersome hot flashes for at least one month (defined as hot flashes that occurred at least seven times per week and were sufficiently severe that the patient desired therapeutic intervention). Life expectancy of six months or more

Tamoxifen (20mg per day) was permitted

Exclusion criteria Current or planned therapy with antineoplastic chemotherapy, androgens, estrogens, progestational agents, or corticosteroids. Women who were breast-feeding and those with child bearing potential.

Population

Number of patients = 166 originally in RCT

Number of patients = 141 contacted for telephone interview (9 were deceased)

Number of patients = 132 provided information for analysis (74 men and 58 women)

Interventions After one week pre-treatment observation period, the patients received megestrol acetate (Megace) 20mg twice daily for 4 weeks followed by placebo for four weeks, or vice versa as determined by randomisation

Outcomes

Number of patients continuing to take megestrol acetate 3 years after RCT completion

Doses being used for long term treatment

Incidence of “breakthrough” hot flashes in this patient population

Reasons for discontinuing megestrol acetate

Follow up Patients contacted 3 years after RCT

Results

OUTCOME OF INTEREST	OVERALL RESULT
Number of patients continuing to take megestrol acetate	55% of the men
Percentage of patients using specific dose of megestrol acetate (no separate results for men and women)	160mg/day (2%) 80mg/day (4%)

	40mg/day (19%) 30mg/day (2%) 20mg/day (42%) <20mg/day (32%)
Number of patients with “breakthrough” hot flashes	24/59 patients Of these, 14 (8 men, 6 women) stated that hot flashes were infrequent and mild. 10 patients experiencing daily hot flashes (3 of these noted several hot flashes per day, occasionally severe).
Spontaneous reporting of side effects (no separate results for men and women) - episodes of chills once hot flashes eliminated	25 patients
- appetite stimulated	9 patients
- weight gain	16 patients
- abnormal vaginal bleeding	5/18 (28% women continuing the drug)
Number of patients who discontinued drug (no separate results for men and women)	73/166 (55%)
Reasons for discontinuation	
- no perceived benefit	17
- vaginal spotting/bleeding/cramping	14
- Taking too many other drugs	13
- hot flashes resolved	12
- weight gain/appetite stimulation	9
- other	16

General comments –

In the RCT “crossover analyses had to be ignored because of significantly difference carryover effects, reflecting a persistent reduction in hot flashes during the placebo period in the patients who received megestrol acetate first”.

Only results for the first 4 weeks were used.

Tamoxifen use was permitted which may affect results.

Same trial as Loprinzi 1994.

Authors conclude a substantial proportion of patients continue to use megestrol acetate for

periods of up to 3 years or longer with continued control of hot flashes. The treatment appears to be relatively well tolerated.

Publication reports results of telephone interview following RCT (see Loprinzi 1994)

Health Economic Summary

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.

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Appendix B Position Paper: Some views on radiation toxicity mechanisms, symptoms, aetiology and prevention

Some views on radiation toxicity mechanisms, symptoms, aetiology and prevention

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1. Introduction

Scope

This paper discusses issues related to external beam radiotherapy for prostate cancer and not brachytherapy.

Availability of data

The data available do not always relate to patients who have undergone radiotherapy for prostate cancer, so data are sometimes presented in this paper which relate to patients who have undergone radiotherapy for other types of cancer but in whom the mechanism(s) / lessons are probably also applicable to patients who have undergone treatment for prostate cancer. Where data from other patients groups is used, this is highlighted.

Definitions: what is radiation toxicity?

It is generally not appreciated that gastrointestinal symptoms following radiotherapy develop as a result of 3 potentially different pathological processes.

1. the development of fibrosis within the gastrointestinal wall, surrounding stroma and mesenteries
2. damage to specific neurological, enzyme based and muscular functions (and probably also local hormonal regulation) of the gastrointestinal tract
3. interaction of acute inflammatory processes or chronic ischaemic and fibrotic processes with preexisting or new causes for symptoms unrelated to radiotherapy.

Fundamental concept when considering toxicity issues

1. Different ***pathological processes*** within the gastrointestinal tract can produce the same ***clinical symptoms***.
2. Conformal radiotherapy to the prostate alone, to the prostate and pelvis and the use of intensity modulated radiotherapy (IMRT) are likely to lead to different types of injury because of the different areas of the gastrointestinal tract which are exposed to some radiotherapy during treatment. However, it is wrong to believe that conformal radiotherapy to the prostate alone never causes small bowel toxicity or damage to areas of the gastrointestinal tract other than the rectum.

2. Mechanisms - Fibrosis

Fibrosis probably develops within the human gastrointestinal tract following radiotherapy as a result of microvascular ischaemia. Of all the late effects of radiation therapy, radiation-induced fibrosis is probably the most extensively studied, although almost all data comes from animal models which are poorly representative of what occurs in humans after radiotherapy (1).

Development of fibrosis

Most men who are to undergo radiotherapy for prostate cancer will have normal bowels. During the five or six weeks of radiotherapy, an acute inflammatory reaction is seen in the parts of the gastrointestinal tract which are exposed to radiotherapy. The changes may vary a great deal between individuals. There have been only very few studies which have characterised the changes in humans in the acute setting. All of these studies have examined changes in the rectum. Changes in the human small bowel during radiotherapy have not been studied. Acute changes are most prominent in the mucosa. Late change develops 3-6 months after the end of treatment and are most prominent in the submucosa.

Histological evidence

Five small series have reported that the rectal acute response following radiotherapy is loss of lamina propria lymphocytes followed by an inflammatory process characterised by an invasion of the epithelium by neutrophils and eosinophilic granulocytes. By 2-4 weeks, eosinophilic micro-abscesses or infiltrates extending from the surface to the submucosa have formed and sometimes persist in patients with progressive changes (2-6). Macrophage infiltration is sometimes reported. Prominent vascular involvement and early fibrotic changes may occur, but are not universal (4) and it is not known whether these are patients who will go on to develop significant problems. Initially, endothelial cells separate from the basement membrane and blood vessel walls dilate with platelet clusters and thrombi in the vascular lumen. Subsequently, after some months, arterioles and venules become narrowed with subintimal fibrosis and fibrinoid necrosis and the reduced numbers of capillary endothelial cells appear to proliferate abnormally, contributing to vessel occlusion (7). Two studies, predominantly including patients who received higher daily doses of radiation than is current practice have noted that maximal rectal histological changes are present at 2 weeks but despite continuing radiotherapy may improve a little over the next 4 weeks. There are no data regarding the development of inflammatory changes earlier than 2 weeks.

Mechanisms and mediators

Different animal models respond differently to identical irradiation (8). So it is unclear how relevant animal models are to humans. Despite this, almost all the information available regarding the cellular and molecular mechanisms of gastrointestinal tractfibrosis are derived from animal experiments. These studies have revealed sequelae of events where early oedema progress into an acute inflammatory reaction. This leads to regenerative processes which either precede mucosal repair or develop into ulceration with severe inflammation which finally leads to fibrosis (8).

Mediators of radiation-induced inflammation in the murine gastrointestinal tract include IL1 beta, IL6, TNF alpha, Transforming Growth Factor (TGF) beta 1 and PDGF (9). There is some evidence that these cytokines are produced by several cell types including macrophages, polymorphonuclear cells, lymphocytes and fibroblasts as well as by the extra-cellular matrix. In the chronic phase, mast cells may also be a source of TGF beta (10). TGF beta is also important for fibrosis after radiotherapy in the human gastrointestinal tract (11) as is connective tissue growth factor (CTGF) (12). However, there are no data about other cytokines or growth factors such as endothelin-1, which are likely to play a role and very limited information about the cell types from which these factors are derived in human patients. In addition, the T helper response, which may alter the fibrotic reaction in the

gastrointestinal tract- it is important in other diseases (13)- has also not been explored in irradiated humans or animal models.

Risk factors

Acute injury to the gastrointestinal tract during radiotherapy partly depends on the dose delivered to the tissues but may also depend on several other factors. A few patients may be very sensitive to small doses of radiotherapy because of a genetic predisposition. Abnormalities in gene expression may alter an individual's capacity to repair damaged DNA. Changes in the ataxia telangectasia, BRCA1, BRCA2, DNA ligase IV, TGF beta 1, XRCC1, hHR21 and NBS genes have been suggested as possible causes for genetically determined normal tissue hypersensitivity to radiotherapy. It has been postulated that conditions such as diabetes, hypertension or smoking - perhaps because these lead to relatively reduced blood flow - previous pelvic inflammatory disease or surgery - perhaps because of the resultant adhesions - HIV disease, connective tissue diseases and inflammatory bowel disease all increase the risk of acute problems. Chemotherapy given just before or together with radiotherapy may sensitize normal tissues to damage from the radiotherapy. It has also been hypothesised mainly on the basis of animal experiments, that the initial insult from radiotherapy induces mucosal changes in the gastrointestinal tract which are then made worse by direct toxic action of bowel contents – especially bile acids and pancreatic secretions. However, to date there are no adequate prospective studies or even retrospective data evaluating the degree of risk posed by any of these factors in prostate cancer patients and the real impact of these factors remains a matter entirely of conjecture.

Progressive and severe late fibrosis

The progressive nature of late fibrosis is demonstrated by studies which suggest that serious toxicity (eg perforation, bowel stenosis) increases with time following treatment. These studies have not been performed in prostate cancer patients however it is likely that similar mechanisms occur (14, 15).

3. Gastrointestinal Functions

The gastrointestinal tract is a sophisticated organ that contains more neurones than the brain and relies on complex neurological, muscular, hormonal and enzyme systems to maintain its secretory, absorptive and propulsive functions. A number of abnormalities of gastrointestinal physiological function can develop during radiotherapy.

Acute changes in gastrointestinal function

Acute changes will potentially occur in any part of the gastrointestinal tract which is exposed to the passage of the beam of radiation. It is controversial whether they persist long term or whether stem cells within the gastrointestinal tract are able to repair the mechanisms which lead to these problems. Probably, in most patients, acute physiological changes will resolve with time. Some physiological changes may lead to clinical symptoms, others may remain subclinical. It is often easier in clinical practice to measure histological changes (by endoscopic guided biopsy) than physiological functions. In other inflammatory bowel conditions, such as Crohn’s disease, histological changes do not correspond well with symptoms. There are no studies which have correlated histological change with symptoms after radiotherapy. However, if a patient develops symptoms during radiotherapy, they tend to start during the second week of treatment, peak by the fifth week and subsequently improve or remain stable. Depending on the sensitivity of the questionnaires used, at least 76% of prostate cancer patients develop some symptoms during treatment and up to 24% say that these prevent them from doing activities which they would otherwise have done. Up to one third of patients report anxieties about how their bowels might behave.

Chronic changes

Potentially many chronic changes to gastrointestinal physiology can occur. In many patients but not all, these physiological changes probably are a major cause of symptoms. It is controversial whether such changes are permanent, some could be reversible. There is evidence that in the majority of symptomatic patients there is more than one cause for the symptoms (16). Many of the studies listed below have been performed in patients treated for pelvic diseases other than prostate cancer. However, there is little reason to believe that different mechanisms will operate in prostate patients compared to patients with other tumours and it is likely that what is important is whether the relevant section of gastrointestinal tract is exposed to sufficient radiotherapy:

- lactose intolerance (17)
- fat malabsorption due to lymphatic obstruction (18)
- bile malabsorption (17)
- changes in motility (17)
- small bowel bacterial overgrowth develops (19, 20)
- pancreatic dysfunction (21, 22)
- changes in the anal canal endovascular cushions (23)
- changes in the anal sphincters (24),
- altered nerve conduction controlling pelvic floor or gastrointestinal tract wall muscles (7, 25, 26)
- changes in rectal compliance (27)
- stool consistency or gastrointestinal motility (28).

It is likely that a number of specific alterations in GI functions after pelvic radiotherapy have nopt yet been identified.

Radiotherapy planning, field size and shape

Under normal circumstances, the gastrointestinal tract is highly mobile - unless there are extensive adhesions following previous surgery or sepsis. It is therefore unlikely that a single scan at the planning stage will predict with complete accuracy which parts of the gastrointestinal tract will enter the radiotherapy field during the course of treatment. Patients who receive Intensity Modulated Radiotherapy (IMRT), conformal radiotherapy to the prostate only or irradiation which includes the whole pelvis as well as the prostate, are highly likely to be at risk of damage to different types of function within the gastrointestinal tract. It is not known what doses of radiotherapy will lead to changes in specific functions.

There are no studies which have examined the effect of radiotherapy on gut hormones although it is likely that some clinical syndromes develop as a result of radiation affecting hormone secretion or the sensitivity or numbers of receptors.

4. Intercurrent Morbidity

In general, gastrointestinal symptoms arise for many reasons. Many patients receiving radiotherapy are elderly. Many elderly patients have clinical or subclinical, pre-existing gastrointestinal disease which may be destabilized by the addition of minor gastrointestinal changes induced by the radiotherapy. The psychological impact of the cancer and the problems induced acutely during treatment may be sufficient in their own right to cause long term significant gastrointestinal tract dysfunction.

Incidence of gastrointestinal toxicity

Prospective studies

There are no prospective studies in patients treated with radiotherapy for prostate cancer where the primary end point is the severity of long term gastrointestinal toxicity. Figures reported for the incidence of gastrointestinal toxicity following radiotherapy for prostate cancer range from 29-45% grade 1 toxicity, 5-14% grade 2 toxicity, 0.6-3% grade 3 toxicity and 0-1% grade 4 toxicity (29-34). However, these figures are derived from studies designed to compare the effectiveness of different treatment regimens in their anti-cancer activity, and reported 2 – 5 year toxicity as a secondary end point, generally using the inadequate measures of toxicity, almost exclusively scored by physicians not patients. In these studies, toxicity appears to be maximal in most patients by 18 months and subsequently either improves or remains at the same level.

Retrospective studies

Retrospective studies may reflect the inherent bias of non-prospective data collection, such as: 1) the different effects produced by different treatment techniques and doses in different groups of people and 2) the different tissue toxicity and responses in different disease states. Despite this, some of the retrospective studies are very patient-centred rather than physician-centred, and give strong support to the view that radiation-induced gastrointestinal toxicity is significantly more common than the prospective data suggest. Retrospective studies suggest that up to 40% of patients have bowel symptoms, and that between 17 - 36% of patients (35-39) report these symptoms as moderate or severe. However, these studies may reflect the outcome from now outmoded radiation techniques. A more recent study suggests that 15% patients regularly worried about the location of the nearest lavatory, whilst 9% cancelled activities because of their bowels (39).

Toxicity requiring surgical intervention

In addition, an as yet unquantified proportion of patients will be at risk of life threatening adverse effects such as transfusion dependent bleeding, fistula formation, deep rectal ulceration and or stenosis. The risk of these complications probably increases with time (14, 15) because they arise as a result of the progressive nature of radiation-induced gastrointestinal fibrosis (section 2.5 above).

Radiotherapy-induced secondary cancer

There is no doubt that radiotherapy can induce cancer. Several large studies have described the risk of second malignancy following the diagnosis of prostate carcinoma. One study was unable to detect any increased risk (40). However, another found a significantly increased risk of colon and rectal cancer less than 5 years after radiotherapy (41), a third an increased risk of rectal (but not colonic) cancer, but only after at least 10 years (42). A recent fourth study suggested that an increased risk was present after 5 years but only in those parts of the gastrointestinal tract which were included in the radiation field. So non-irradiated parts of the colon were not at increased risk (43). It may be of relevance that large studies of second cancers after treatment for cervical cancer found a significant increase in rectal carcinoma after radiotherapy, but not cancer of the colon (44, 45). Other authors have putatively advocated surveillance for colorectal tumours after pelvic irradiation for gynaecological cancers (46, 47).

Problems with toxicity scoring

Historically, radiation oncologists have relied on patients completing a questionnaire to measure toxicity. This method of measuring toxicity is perhaps best exemplified in an important paper by Denham et al which suggested that prostate radiotherapy resulted in 5 different types of “proctitis” syndromes (48).

However, the use of questionnaires to measure toxicity is inadequate for the following reasons:

Different *pathological processes* can produce the same *clinical symptoms*

Questionnaires may not pick up background gastrointestinal morbidity which predates the radiotherapy and may include it as new onset symptoms

Patients may not answer questionnaires truthfully especially when they are physician scored. There is excellent evidence that physicians and patients score the impact of their symptoms quite differently. All current, widely-used radiotherapy toxicity questionnaires are physician scored.

Reasons for non-reporting of symptoms amongst patients include:

- They often believe that their symptoms are the inevitable consequences of radiotherapy treatment, of being old or that there is nothing that can be done (49)
- They believe there are more important issues to discuss in the limited time available (38).
- They do not want to appear ungrateful (50)
- They do not see the relationship between their symptoms and treatment
- They do not understand the questions (50). For example, while patients may freely admit to diarrhoea, fewer than 50% will admit to faecal incontinence, unless they are asked very directly whether this is happening (51, 52). Women are more likely to report faecal incontinence than men (personal communication RL Nelson, Chicago).
- Questionnaires do not ask the appropriate questions eg RTOG does not ask about anorectal symptoms.

Different pathological processes produce the same symptoms

Attempts to measure the incidence of significant late symptoms induced by radiotherapy are confounded by the fact that different pathological processes can produce the same symptoms. For example, several series have shown that the nature of rectal bleeding after prostate radiotherapy does not reliably predict the underlying cause of the bleeding:

Author	Year	N=	Findings on endoscopy	N=with prostate ca
Reichelderfer	1980	13	colonoscopy changes Mx	0
Den Hartog Jager	1985	90	25% unrelated to RT	7
Moore	2000	26	65% unrelated to RT	26
Wachter	2000	44	c25% unrelated to RT	44
Williams	2005	171	symptoms are an unreliable guide to the underlying pathology and 33% unrelated to RT	133

(RT = radiotherapy)

Data from several papers suggest that it may not be valid to categorise many patients' problems within a syndrome labelled as "radiation proctitis" or "radiation enteritis". Symptoms arise in these patients not from specific syndromes but from specific functional changes suggesting that symptoms in general, are not a reliable way of defining the underlying pathology. For example, diarrhoea after radiotherapy may be caused by at least 13 different mechanisms reflecting changes in widely separate parts of the gastrointestinal tract (16, 19, 53-55)

Conclusion

Two studies have suggested that patients with radiation-induced symptoms should undergo investigation following an algorithm (16, 56) since new onset symptoms after radiotherapy may be due to more than one cause and also are not necessarily due to radiotherapy treatment. The outcome of therapies for "radiation proctitis" have been summarized in a recent Cochrane review (57).

5. The Prevention of Toxicity

It is difficult to prevent gastrointestinal toxicity efficiently if the true frequency of toxicity is not known, the optimal methods for measuring toxicity are not agreed and there is almost no insight into the pathological mechanisms which cause it.

One important but yet unproven concept, is that of "the consequential effect". This suggests that the severity of the acute response to radiotherapy predisposes to increased late toxicity. If correct, this suggests that the prevention of acute side effects should be a priority (58).

The prevention of small bowel toxicity

A number of interventions may be useful:

Nutritional intervention

The options are summarised in a recent systematic review (59). A 100% elemental diet would seem the most promising approach based on animal studies but there are no convincing human data to support this as an intervention to date. Other options include dietary fat manipulation, the use of prebiotics or probiotics and the use of fibre to produce protective short chain fatty acids.

The belly board

There are no studies in prostate cancer patients and the methodology needs more basic research.

Drugs to reduce acute toxicity (and hence "the consequential effect"?)

One human study has demonstrated reduction of acute symptoms from the use of octreotide (60). This study did not provide any long term follow up data. Previous animal studies have suggested that the use of octreotide during radiotherapy improves both acute and chronic toxicity. Other studies using glutamine supplements and sucralfate suggest that these substances do not convey benefit acutely.

Prevention of toxicity anywhere within the bowel

Intervention with anti-fibrotic medication

Since damage to gastrointestinal tract function occurs through a poorly defined, pro-fibrotic mechanism, early intervention before the fibrosis has developed may reverse the loss of function that progressive fibrosis causes. Studies have clearly demonstrated that fibrosis can be reversed in other circumstances such as in cirrhosis of the liver or ameliorated in the skin after radiotherapy. Many therapies have potential anti-fibrotic activity. They include:

Some human data
liposomal Cu/Zn superoxide dismutase
pentoxifylline +/- high dose vitamin E
hyperbaric oxygen
Animal data only
ACE inhibitors
colchicine
endothelin-1 antagonists
integrin antagonists
interferon α or γ
PDGF antagonists
TGFß antagonists
TNF α antagonists

Intervention with anti-ischaemic agents

Fibrosis probably occurs because of the ischaemia induced by the occlusion of the local microvascular circulation as a result of radiotherapy. There is no evidence that any intervention is useful to date. Animal studies suggest that anti-platelet agents and anticoagulants may have different effects. This has not been studied in man, almost all the studies in this area have been conducted by Martin Hauer-Jensen's group.

Miscellaneous drugs

Amifostine: The evidence has been summarised in a recently updated systematic review. This radioprotective agent is recommended in this study only for patients receiving radiotherapy for rectal cancer (level III evidence, recommendation grade B) (61).

Misoprostol: not beneficial in the only randomised controlled trial performed and potentially may lead to increased rectal bleeding and tumour growth (62)

Anti-inflammatory agents: The evidence has been summarised in a recently updated systematic review, these drugs are theoretically useful but there are no clinical trials showing clear benefit (63).

6. Conclusions

Of all side effects of radiotherapy, gastrointestinal toxicity has the greatest adverse effect on quality of life in prostate cancer patients treated with radiotherapy (64).

The terminology in current usage is not correct and should be abandoned. “Radiation proctitis” or “radiation colitis” or “radiation enteritis” imply “inflammation” by the use of the ending –itis. Inflammation only occurs to a significant degree in the acute setting. In the late phase, inflammation is largely absent and if a generic term is required to describe a syndrome, the terminology used should be “radiation proctopathy” or “radiation colopathy” or “radiation enteropathy”. However, the concept of “radiation syndromes” may be misleading and patients might be better helped if symptoms were viewed in terms of potential loss of specific gastrointestinal functions.

There has been an astonishing degree of complacency and lack of research into radiation-induced gastrointestinal tract injury by oncologists and gastroenterologists

There appears to be a marked lack of appreciation by the medical community in general and oncologists in particular, how debilitating gastrointestinal symptoms after radiotherapy can be. This partly results from the poor quality of the tools used by oncologists to measure symptoms.

Most oncologists and many gastroenterologists fundamentally fail to understand why patients develop gastrointestinal symptoms after pelvic radiotherapy and there is almost no attempt to identify these patients in follow up clinics systematically, and when identified, there are hardly any established pathways to which these patients can be directed for investigation and effective treatment. In the absence of medical help for these patients, there is also an almost complete lack of information for patients to undertake self-help programmes.

There are a very large number of nutritional and therapeutic interventions which may help reduce the frequency of radiation injury occurring. Almost none have been tried in humans. Many are simple, safe and established treatments in other contexts, which would be relatively inexpensive to investigate.

Patients with radiation-induced gastrointestinal symptoms often have other pelvic problems, related to the bladder and / or sexual function and these can have significant emotional, physical, psychological, economic and social ramifications (34-37, 64-66). Therefore, radiation induced bowel damage should not be considered in isolation from these other issues.

It is likely that in the patient with symptoms, that systematic investigation of those symptoms will produce evidence of clear functional abnormalities within the gastrointestinal tract which may respond to specific treatments.

Rectal bleeding in these patients should be routinely investigated with flexible endoscopy

Patients should be considered for flexible sigmoidoscopy screening for colorectal cancer once they are 5 years after treatment

The use of steroid enemas for proctopathy-type symptoms are probably unhelpful. The lack of trials proving that other treatment work, does not mean that treatment is ineffective. It simply is a reflection of the medical community's lack of interest in this area (57).

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